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A COMPARISON BETWEEN THE CLINICAL EFFECTS OF PYRIBENZAMINE AND THOSE OF BENADRYL*

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NEW YORK CITY

ALTHOUGH twenty articles on the clinical effects of Benadryl have appeared in the American literature since early in 1946, when the drug was introduced, only five are to be found on Pyribenzamine. Feinberg and Friedlaender[1, 2] are the only investigators who have made serious inquiry into the practical value of both drugs, and no statistics are available on the relative efficiency of these two agents in the same subject. Furthermore, their prophylactic and therapeutic possibilities in "constitutional" reactions to overdosage of allergenic extract have been examined in only 8 cases.[3] The purpose of the present report is to add observations on Pyribenzamine in 150 adult patients and on the practical use of Benadryl in 53, including cross-trials in 33 cases and the treatment of "constitutional" reactions with the histamine antagonists in 20.

MATERIALS AND METHODS

A majority of the patients were inpatients or outpatients complaining of hay fever, bronchial asthma or acute (often drug) urticaria, whereas a few had atopic dermatitis, chronic urticaria, dermographism or acute serum reaction. Sixteen patients who had developed hay fever, asthma or cutaneous allergy directly after an overdose of therapeutic allergen were given one of the two antihistaminic drugs orally on twenty such occasions to determine its value.

The dose routinely prescribed was 50 mg. by mouth, to be repeated in one to four hours if symptoms persisted or recurred but not oftener than five times in any twenty-four-hour period. Usually, one such dose sufficed to control the symptoms for four hours, so that few patients ingested more than two or three a day. The drugs were restricted to symptomatic relief and were never employed prophylactically. Many of the trials were initiated under our direct supervision or that of assistants, so that the results might be judged objectively as well as subjectively.

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RESULTS

Clinical Effectiveness

Constitutional reaction. The disorder most susceptible to the drugs appeared to be the constitutional reaction that follows overdosage of allergic patients. If such responses were not of violent intensity, they almost invariably diminished or disappeared twenty or thirty minutes after the oral administration of 50 mg. of the histamine antagonist. The blanching of a brilliant erythema and the diminution of acute urticarial wheals were usually too rapid, once initiated, to resemble spontaneous resolution. Asthma was relatively refractory to the drugs as compared to nasal or cutaneous manifestations (Table 1).

Twelve cases of mild systemic reaction were treated with Pyribenzamine. Three subjects who developed generalized erythema and slight wheezing lost the cutaneous signs and most of the bronchospasm twenty minutes after ingesting 50 mg. of the drug. Three others had similar manifestations, which were completely controlled. Another patient, with accidentally induced hay fever, showed complete recovery half an hour after the taking of a 50-mg. tablet, and a similar case was partially relieved. Pruritus of the eustachian tube and facial erythema that had followed an overdose yielded partially to a tablet of Pyribenzamine. The urticarial eruptions of 3 pollen-inoculated subjects responded spectacularly to the drug, and another patient required two hours for the clearing of the skin. Thus, there were complete responses in 8 and partial responses in 4 cases to a single 50-mg. dose of Pyribenzamine in 12 patients with constitutional reactions who received no other treatment (Table 1).

The situation with accidentally induced asthma was less encouraging. When bronchospasm occurred

shortly after an inoculation of allergenic extract and was of marked intensity, Pyribenzamine was without effect in 2 of 4 cases. Adrenalin, however, brought prompt relief.

The 4 cases of systemic reactions treated with Benadryl by mouth appeared to respond as well as those treated with Pyribenzamine.

Acute urticaria was next in order of susceptibility to the antihistaminic agents. There were 27 cases of acute drug allergy, 21 being referable to penicillin and 2 to sulfonamides. Four patients lost not only the subjective discomfort but also the lesions. Eighteen ceased to itch and showed diminished cutaneous signs. One case of phenobarbital and 1 of novocain hypersensitivity showed partial improvement, whereas a streptomycin rash and an exfoliative dermatitis due to gold therapy resisted all antihistamine therapy. Acute urticarial eruptions of unknown etiology in 2 of 4 cases responded spectacularly.

Successful attempts were made to control acute urticaria with Benadryl in 2 cases. Chronic urticaria yielded to treatment in over half the trials with the two drugs.

Allergic rhinitis of extrinsic seasonal variety (pollen hay fever) responded almost as well as the drug eruptions. Some of the patients in this class had received preseasonal therapy against ragweed hay fever. All were given small supplies of one of the drugs for use at such times as symptoms developed. Eighty-five per cent of the 60 patients in this group reported success with Pyribenzamine; 19 of these were subsequently given Benadryl for comparison, and all but 4 found the drugs equally effective. Nineteen other subjects were tested clinically with Benadryl alone and experienced relief comparable with that described after Pyribenzamine.

In another group of 8 patients with nonseasonal allergic rhinitis similar tendencies to yield to the drugs were shown in 6 cases. The number of observations was obviously too small for definite conclusions. This paucity of sampling likewise applies to the remainder of the data, which are presented mainly to add to the still inadequate figures available in the literature.

Other conditions. Extrinsic asthma treated with the drugs showed improvement in 7 of 11 cases, and intrinsic asthma responded partially in 3 of 9 cases. Of the 20 cases in which observations on asthma of all types were made, 50 per cent yielded to drug therapy, but in most cases the improvement was partial. Atopic dermatitis was even less responsive, the results being entirely negative in 4 patients and partial in 1, who noted that the pruritus was controlled. One of 2 subjects with pruritus due to obstructive jaundice also considered the subjective discomfort to have been alleviated after the administration of Pyribenzamine. The wheal, flare and pruritus of dermographia were reduced if two tablets were administered fifteen minutes before the skin was traumatized with a fingernail stroke. Similarly, the drug afforded definite relief to a young woman who had developed generalized urticaria, angioneurotic edema and critical hypotension a few hours after having received antitetanic horse globulin; the intense itching and the tendency for the arterial tension to drop to shock levels were both controlled by hourly doses of 50 mg. administered for four hours.

In general, the experience with these drugs makes it appear that they are most valuable in urticaria, hay fever and in systemic reactions to overdoses of allergenic solution.

TABLE 1. *Comparative Results of Histamine Antagonists in Allergic Disorders.*

Disorder	Results with Pyribenzamine				Results with Benadryl			
	Complete relief	Partial relief	No relief	Total patients relieved	Complete relief	Partial relief	No relief	Total patients relieved
Allergic rhinitis:								
Extrinsic seasonal (hay fever)	27	24	9	51 (85%)	14	17	7	31 (82%)
Extrinsic nonseasonal	3	1	2	4 (67%)	2	0	0	2 (100%)
Intrinsic	2	0	0	2 (100%)	0	0	0	0
Asthma:								
Extrinsic seasonal	0	0	1	0	0	1	0	1(100%)
Extrinsic nonseasonal	2	4	2	6 (75%)	0	0	1	0
Intrinsic	0	3	4	3 (43%)	0	0	2	0
Urticaria, acute:								
Due to drug	4	20	3	24 (89%)	0	2	0	2 (100%)
Due to other factor	2	0	2	2 (50%)	0	0	0	0
Urticaria, chronic	3	3	6	6 (50%)	1	0	0	1 (100%)
Dermatitis, atopic	0	1	2	1 (33%)	0	0	2	0
Pruritus	0	1	1	1 (50%)	0	0	0	0
Constitutional reaction:								
Mild	8	4	0	12 (100%)	2	1	0	3 (100%)
Moderately severe (asthma)	2	0	2	2 (50%)	0	1	0	1 (100%)
Dermographism	0	1	0	1 (100%)	0	0	0	0
Serum reaction	0	1	0	1 (100%)	0	0	0	0
Totals	53	63	34	116 (77%)	19	22	12	41 (77%)

Relative Efficacy in the Same Patient

Figure 1 indicates the results of trials in 33 patients in whom the effects of first one drug and then the other were established. In 23, the therapeutic influence of the two agents could not be distinguished. Among the remainder, half preferred one and half the other medication. In the group in which equal response to either drug was reported 4 patients detected no influence on their complaints, 7 reported partial control of symptoms, and 12 were completely relieved. So far as the type of complaint is concerned, 20 subjects in this experiment were ragweed sensitive, 3 exhibited systemic reactions to therapeutic injections, and the remainder were given the histamine antagonists for such conditions as intrinsic asthma, atopic dermatitis and acute and chronic urticarial eruptions.

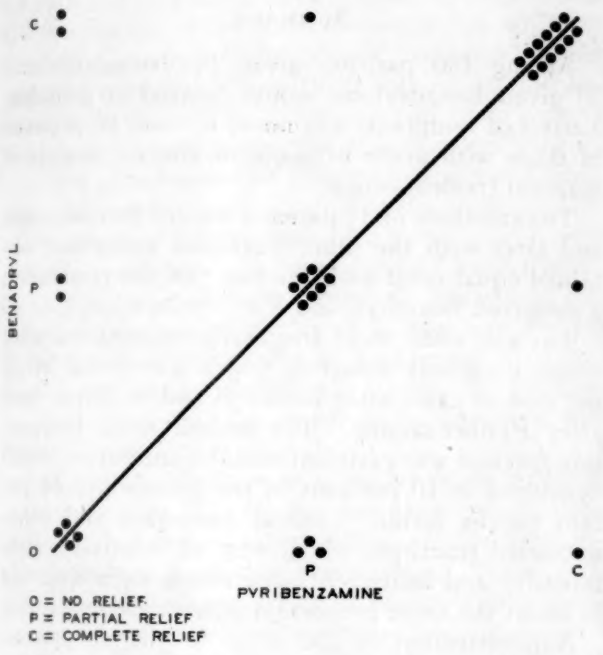

FIGURE 1. *Relative Efficiency of Pyribenzamine and Benadryl in Thirty-Three Patients.*

Side reactions. Proportionately, nearly twice as many patients had untoward reactions from Benadryl as from Pyribenzamine (Table 2). Some patients noted more than one side effect. The complaint most frequently observed was drowsiness associated with mental sluggishness. Whereas 61 per cent of patients treated with Benadryl were afflicted in this way, only 20 per cent of those treated with Pyribenzamine gave evidence of sedation. Gastrointestinal disturbances, ranging from nausea, anorexia and epigastric distress to vomiting, diarrhea and abdominal colic, were encountered somewhat oftener after Pyribenzamine than after the other drug. A sense of exhaustion and generalized weakness occurred after 8 per cent of the Benadryl treatments, whereas only 3 per cent of patients treated with Pyribenzamine had this type of side effect. Central stimulation caused insomnia and sensations of nervous tension in 4 per cent of both groups. There were 2 cases of headache, both related to Pyribenzamine. Dizziness was reported by 6 per cent of patients given Benadryl and by 3 per cent of those treated with Pyribenzamine. Muscle twitchings, tenderness and aches and in some cases difficulty in phonation and in co-ordinating movements of the extraorbital muscles were described by 6 per cent of the former group and by 2 per cent of the latter. One patient in each series complained of feeling depressed. An occasional case of numbness of the lips and tongue was detected; the condition was ascribed to the local anesthetic action of both drugs. One patient believed that Benadryl provoked a cough lasting for several days, and another was certain that a pre-existing asthmatic cough had been exaggerated shortly after the taking of Pyribenzamine. The former has been listed under the heading of "hypersensitivity" for want of a better classification.

TABLE 2. *Side Effects of Histamine Antagonists in 178 Cases.*

Side Effect	With Pyribenzamine		With Benadryl	
	No. of cases	Per-centage	No. of cases	Per-centage
Drowsiness	26	20	31	61
Gastrointestinal upset	18	14	5	10
Exhaustion	4	3	4	8
Excitement and insomnia	5	4	2	4
Dizziness	4	3	3	6
Faulty co-ordination of vocal or extraorbital muscles; twitching and pains	3	2	3	6
Headache	2	2	–	–
Depression	1	1	1	2
Numb lips and tongue	2	2	1	2
Tinnitus	1	1	–	–
"Hypersensitivity"	–	–	1	2
Exacerbation of cough	1	1	–	–
Totals	67		51	
Percentages of total cases treated		40		71

Discussion

There seems little doubt that the histamine antagonists are of definite value in the symptomatic relief of acute urticaria and of seasonal hay fever. Their value in the prevention or control of manifestations due to overdosage with therapeutic allergens is difficult to appraise. If, as in the experiments of Arbesman,[3] the drug is given shortly before the "overdose," there is always the possibility that on this particular occasion the dose would have been tolerated even without the drug. On the other hand, if one awaits the development of systemic manifestations, the drug must be allowed fifteen to twenty minutes for its effect to become apparent. Obviously, such delay would be unwarranted if the situation was at all critical.

One is limited, therefore, to studying the new drugs in cases of relatively mild systemic reaction. Under these circumstances, judgment is clouded by the tendency of mild overdosage reactions to subside spontaneously after twenty or thirty minutes.

Theoretically, it might be expected that such overdosage symptoms as urticaria, hay fever and histamine-like hypotension would be counteracted by the drugs. If bronchospasm developed, however, it would be anticipated that they would prove less effective. Our limited experience with overdosage reactions seems to be in keeping with these theories. It seems probable that the simultaneous administration of adrenalin intramuscularly and of a histamine antagonist orally would ensure prompt relief and sustained control of symptoms other than asthma. In the latter situation it might be wiser to replace the antihistamine drugs with Neo-Synephrin or some similar, orally administered antispasmodic.

Although seasonal hay fever and other extrinsic types of vasomotor rhinitis are symptomatically relieved by the new drugs in a high proportion of trials, the most satisfactory management of hay fever appears to rest on a combination of specific therapy and of symptomatic relief with the antihistaminic agents. Many of the patients came to this conclusion by the end of the 1946 ragweed pollinating season, whether they had omitted their customary "booster" courses and had depended on the drugs alone or had taken injections and employed the drugs only occasionally when necessary. The new drugs play their most valuable role in acute and even in some cases of chronic urticaria because no other satisfactory remedies are available. This remark also applies to such cases of bronchial asthma as respond to Benadryl or Pyribenzamine.

There are important differences in the types and incidences of side reaction that follow the two drugs. Although Benadryl produced sedation in 60 per cent of patients, this fact may be turned to advantage when fatigue, anxiety or insomnia complicates the allergic disorder. The sedative effect is also highly desirable for pruritus. Benadryl should be deliberately selected in such cases. On the other hand, patients whose efficiency and judgment may be impaired by sedation should be given Pyribenzamine for daytime use. Since gastrointestinal complications follow Pyribenzamine somewhat oftener than they do Benadryl, the latter is probably more suitable for patients with abnormalities of gastrointestinal function. It was our impression that the taking of food with Pyribenzamine or of caffeine or benzedrine with Benadryl obviated some of the side effects.

Whereas most patients given first one remedy and then the other reported comparable results with each, a small group responded selectively. It would be well, therefore, to change to the other drug when one gives rise to either undue side reactions or unsatisfactory therapeutic control.

Summary

Among 150 patients given Pyribenzamine and 53 given Benadryl by mouth, partial or complete control of symptoms was noted by over 80 per cent of those with acute urticaria or allergic rhinitis of seasonal (pollen) origin.

Twenty-three of 33 patients treated first with one and later with the other histamine antagonist obtained equal relief with the two. Of the remainder, 5 preferred Benadryl, and 5 Pyribenzamine.

The side effect most frequently encountered with either drug was sedation, which was noted in 61 per cent of cases after Benadryl and in 20 per cent after Pyribenzamine. The second most frequent side reaction was gastrointestinal disturbance, which developed in 10 per cent of the former and 14 per cent of the latter. Central excitation and other untoward reactions, which were of relatively mild intensity and infrequent occurrence, were observed in about the same proportion of both groups.

Administration of the drugs to allergic persons during "constitutional" reactions in 20 cases produced encouraging results for urticaria, hay fever and mild bronchial spasm, but severer asthma seemed to resist their influence.

The technical assistance of Mrs. Gloria Giarrizzo is acknowledged.

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ACUTE HEMOLYTIC ANEMIA IN PRIMARY ATYPICAL PNEUMONIA PRODUCED BY EXPOSURE AND CHILLING*

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ACUTE hemolytic anemia in the course of primary atypical pneumonia has been reported by Dameshek,[1] Finland[2] and others. Elucidation of the mechanism of this form of anemia has not been offered. Clinical evidence shows that such anemia develops coincidentally with high titers of cold agglutinin in the serum. Since most of these reports have been concerned with patients to whom varying amounts of sulfonamides have been given and since acute hemolytic anemia can develop from the administration of the sulfonamides alone, it has been difficult to exclude the drugs entirely as the cause or to establish the acute hemolytic anemia of primary atypical pneumonia as a separate entity. Ginsberg[3] has reported the occurrence of acute hemolytic anemia during the course of primary atypical pneumonia in which no sulfonamide was given.

The patient in the case reported below received no sulfonamide. The clinical and experimental data indicate that exposure and diffuse chilling were instrumental in producing the anemia. These data are in accord with and are an extension of previously known facts. This mechanism has been postulated by Dameshek[1] and Finland[2] in the reports cited above. Their view was based, at least in part, on evidence that the anemia developed before the administration of sulfonamide and that this therapy did not appear to influence the course of the anemia.

General Considerations

Increased cold-agglutinin titers in this disease were first described by Clough and Richter[4] in 1918. Their patient had a diffuse bronchopneumonia with the usual course and with objective findings of what would now be called a primary atypical pneumonia. They failed to associate the disease and the serologic changes and assumed the cold agglutinin to be a peculiar hereditary trait. Cold agglutinin was present in the serum to a titer of 1:500 at refrigerator temperature. The properties of this cold agglutinin were studied with classic thoroughness, and with the exception of the agglutination of indifferent streptococci by Thomas et al.,[5] little of significance has been added by subsequent studies. Clough and Richter's patient also showed a transient slight depression of the red-cell count and hemoglobin content.

Of particular interest is the report of the inverse relation between the temperature at which the cold-agglutination tests were performed and the degree of agglutination. The titer, which was highest at "ice chest" temperature, became progressively lower at higher temperatures, and agglutination was abolished at 24°C.

In 1926, Li Chen-Pien[6] reported that cold hemagglutinins found in a patient suffering from cirrhosis and syphilis had similar properties to those in the case reported by Clough and Richter. The inverse temperature effect was demonstrated, and the agglutination was negative at temperatures greater than 20°C. The Donath–Landsteiner test was negative.

In 1939, Wheeler, Gallagher and Stuart[7] described a potent cold agglutination in a respiratory infection similar to that reported by Clough and Richter. These authors also failed to associate the disease and the serologic changes. A study of the properties of the cold agglutinin agreed with the findings of Clough and Richter. In particular, a similar inverse relation between the temperature and the degree of agglutination was observed. The titer was 1:10,240 at 4°C., 1:2560 at 12, and 1:160 at 22, and no autohemagglutination was present at 30. This patient did not show anemia.

In 1943, Peterson, Ham and Finland[8] noted the association of powerful cold agglutinins with primary atypical pneumonia. Similar cases were then reported from other clinics.[9, 10] In 1945 Finland and his associates[11] published a report of cold-agglutinin titers in primary atypical pneumonia, in common diseases of temperate climate and in health. A study of the properties of the cold agglutination[12] reconfirmed the findings of Clough and Richter.

Observation of the hemolytic properties of the cold agglutinin began with the work of Salén,[13] who recognized that this hemolysis did not require complement and was therefore quite different from the Donath–Landsteiner hemolysin. Salén demonstrated hemoglobinuria in a subject with powerful cold agglutinins by immersing the legs in ice water. The entire study is difficult to interpret, since Salén did not recognize the role of mechanical trauma in producing hemolysis. His protocol of method calls for thorough mixing of cells and serum by shaking, transferring and centrifuging.

A series of reports by Stats and associates [14–16] presented clear demonstration of the mechanism of hemolysis of erythrocytes in the presence of

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powerful cold agglutinins. Hemolysis was shown to be due to mechanical trauma, such as shaking or tapping, applied to the cold-agglutinated erythrocytes. The degree of hemolysis was directly proportional to the heaviness of the cell suspension and the degree of agglutination. Intravascular cold agglutination was demonstrated in vivo when the tissue was adequately chilled. Hemolysis was shown to occur in vivo after such intravascular cold agglutination.

For details of the ingenious methods employed by these workers, the reports should be consulted. Unfortunately, none of the cases presented evidence of anemia. The inverse temperature relation previously noted was present in the most thoroughly studied case, but in spite of high titers at low temperatures, the temperature of extinction of agglutination was 16°C. Only small parts of the body of the subject were exposed to temperatures below 16°C. either clinically or experimentally. This patient had gangrenous changes in the tips of the extremities as the result of activity of cold agglutinins during severe exposure.[15]

The premise that this mechanism of local hemolysis is the underlying cause of the acute hemolytic anemia associated with powerful cold agglutinins could be tested by reduction of the temperature of a large area of the skin surface and subcutaneous tissue of a suitable human subject to a level at which potent cold agglutinins would be active. This degree of cold might be any temperature from 4 to even 37°C., depending on the temperature at which the cold agglutinin was sufficiently high in titer to produce agglutination and lead to subsequent hemolysis. Temperature ranges of the exposed skin and subcutaneous tissue depend largely on the room temperature and degree of exposure and are usually from 24 to 34°C. After exposure to cold, the skin temperature may fall grossly below this level.[17] Thus, the coincidence of the temperatures of cold-agglutinin activity and of the skin may be easily attainable in certain cases.

In view of the above considerations, the following clinical record approaches an experimental protocol in which the previous hypothetical conditions for development of acute hemolytic anemia were satisfied.

Table 1. *Pertinent Laboratory Data.*

Date	Corrected Sedimentation Rate (Wintrobe)	Mazzini Blood Test	Nonprotein Nitrogen	Serum Bilirubin*			Donath-Landsteiner Test for Cold Hemolysin	Agglutination for Streptococcus MG†	Remarks
				total	free	bound			
	mm./hr.		*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*		*titer*	
3/29	—	—	—	—	—	—	—	—	Sputum culture insufficient for examination; blood culture sterile after 18 da.
3/30	43	—	—	—	—	—	—	—	—
4/5	—	Negative	—	—	—	—	—	—	—
4/9	—	—	29.6	0.61	0.54	0.07	Negative	—	At height of hemolytic crisis, examination revealed patient's blood to be Type B and Rh+; rapid spontaneous agglutination of own cells in own serum at room temperature.
4/10	—	—	28.0	1.10	0.84	0.21	—	—	Patient still in hemolytic crisis
4/12	—	—	—	—	—	—	—	1:20	—
4/22	15	—	—	—	—	—	—	—	—

*Determined by means of DuBoscq colorimeter with use of cobalt sulfate standards.
†Determined by Dr. Frank Horsfall, Jr.

Case Report

A 21-year-old unmarried woman was admitted to the hospital on March 29, 1946, with the chief complaints of malaise, weakness, chills, fever and cough. Three days prior to admission the patient had noticed chilliness, fever and generalized aching. Two days later a hacking cough productive of a small amount of white mucoid material developed. There was no history of blood-tinged or rusty sputum or of pleuritic pain.

Table 2. *Red-Cell Counts and Hemoglobin Data.*

Date	Red-Cell Count	Hemoglobin	Remarks
	x10⁶	*gm./100 cc.*	
3/30	4.10	12.5	
4/1	—	—	Patient given cold sponge bath (ice-cold alcohol)
4/3	3.96	12.0	—
4/7	—	—	Patient given cold sponge bath
4/8	2.07	7.5	Patient given cold sponge bath
4/9	—	—	Patient given three cold sponge baths in early morning
	1.64	4.5	Patient given 1000-cc. transfusion of compatible fresh whole blood
4/10	2.45	6.0	Patient given 1000-cc. transfusion of banked whole blood
4/11	3.34	10.5	Patient given 500-cc. transfusion of banked whole blood
4/12	3.21	9.0	—
4/15	3.31	9.5	—
4/18	3.25	10.0	—
4/20	—	—	Patient given 500-cc. transfusion of banked whole blood
4/22	3.85	11.5	—

The past history revealed that voluntary dietary restrictions had led to the loss of 20 pounds in the 3 or 4 months prior to admission. There was no further clinical history of any significance.

Physical examination was negative except for finely crepitant rales in the lower lobe of the left lung posteriorly.

The temperature was 102.2°F., the pulse 100, and the respirations 22. The blood pressure was 128/78.

The clinical diagnosis was primary atypical pneumonia of the lower lobe of the left lung.

Examination of the blood disclosed a red-cell count of 4,100,000, with a hemoglobin of 12.5 gm. per 100 cc., and a white-cell count of 9900, with 81 per cent adult neutrophils, 16 per cent small lymphocytes, 2 per cent monocytes and 1 per cent basophils. (The total and differential white-cell counts did not change essentially from admission levels during the first 2 weeks in the hospital.) Urinalysis showed nothing remarkable except on one occasion reported below. Table 1 presents the pertinent laboratory data.

Penicillin therapy was begun on the 1st hospital day in doses of 30,000 units every 3 hours, but was discontinued after 3 days because it appeared to be of no value. The fever tended to decrease somewhat until April 4, but on the following day there was an upward swing of the temperature, with a spiking pattern. Progressive pallor and weakness were observed. The nurse's records reported "dark urine," but these specimens were not saved for examination.

On April 8 the clinical and roentgenologic signs of pneumonitis had spread to both lungs. The spleen was enlarged, and the hemoglobin had dropped to 7.5 gm. per 100 cc., with a red-cell count of 2,070,000 (Table 2); the patient passed swiftly and yet imperceptibly into a serious condition. On the same day the red cells, when mixed with the patient's own serum, agglutinated in 10 to 20 seconds at 26°C. The clumping was easily visible on gross inspection and resembled that seen in slide typing with potent agglutinating serum. After eight washings with warm saline solution, the red cells no longer agglutinated spontaneously, and blood typing could be done.

Cold-agglutination tests showed a titer of 1:1280. The titer at 26 was identical to that at 7°C.; the titer at 37°C., however, was only 1:5, and the clumping in the 1:5 dilution was dubious. All agglutination could be dispersed by warming of the tubes to 38°C. (Table 3). During the night the temperature rose to 106°F.

In spite of explicit orders to keep the patient warm, a nurse gave her three general body sponges using iced alcohol. On the following morning the red-cell count had dropped to 1,640,000, with a hemoglobin of 4.5 gm. per 100 cc. The patient looked moribund. A dark-brown urine specimen was reported to have been passed in the morning after the sponges, but had been discarded. The next specimen showed no demonstrable hemoglobin by chemical test.

Between April 9 and 11, a total of 3000 cc. of fresh and banked blood was given. The blood was warmed to 37°C. in a water bath before delivery to the bedside and was kept warm during administration. No reaction occurred. The absence of any reaction may have been of some importance, since intracellular hemosiderin granules were demonstrated in epithelial cells obtained from the centrifuged urinary sediment on April 13. Between April 11 and 17, at the suggestion of a consultant, 100,000 units of penicillin was given intramuscularly every 2 hours.

During this period the clinical evidence of pneumonitis became more obvious, and the titer of the cold hemagglutinins at 7 and 26°C. increased to 1:5120. In spite of this, no further hemolysis occurred, and the patient slowly recovered. Rigid precautions were taken during this period to keep her warm. She was sent home on May 2 with instructions to avoid cold, exposure and tub baths.

The temperature chart is presented in Figure 1. The hemolysis in vitro is shown in Table 4. The hemolysis is interpreted as due solely to unavoidable trauma to the cells.

Experimental Data

On April 30, after recovery had been assured, it seemed safe to perform an experiment. The cold agglutinin titers on that day were 1:2560 at 4°C. and 1:40 at 26, and no agglutination was found at 37.

The right arm was immersed for 15 minutes in ice-cold water containing pieces of ice. The patient voided immediately before the immersion, and this urine was saved for control purposes. A sample of blood was obtained from the left arm immediately before immersion. Every precaution was taken to avert adventitious hemolysis. Blood samples were withdrawn from the right arm 15 minutes after the cessation of immersion (30 minutes after the beginning of immersion). Blood samples were drawn from the same arm at 15-minute intervals thereafter. These blood specimens were labeled 0 (control), 30 minutes, 45 minutes and 60 minutes, respectively. A final specimen was drawn from the same arm 120 minutes after the beginning of exposure. Plans to draw corresponding samples from the left arm had to be abandoned because of residual damage to the veins of this arm as the result of prolonged and intensive intravenous therapy.

After collection of these samples, the blood was allowed to clot at room temperature with no agitation. The serum was separated with great care. The warm tubes were then centrifuged to remove any possible residual cells or particulate material. Except for slight difficulty in obtaining the 30-minute specimen (necessitating repuncture of the vein), the blood samples appeared to have been ideally obtained. The difficulty with the 30-minute specimen did not appear adequate to account for significant hemolysis in it.

The patient voided 1½ and 12½ hours after the beginning of immersion of the arm. All the voidings were saved in a dry, clean container. After thorough mixing, portions of each of these specimens and of the control urine were saved for spectral analyses.

The serum and urine specimens were subjected to spectral analyses* 36 hours after immersion. The 120-minute sample was not tested.

The control and the 120-minute serums were completely free from any trace of hemoglobin on gross visual inspection. The 30-minute specimen was markedly hemolyzed, and the 45-minute specimen showed somewhat less marked hemolysis. The 60-minute specimen showed only the faintest trace of hemolysis, and there was a difference of opinion concerning whether this was actually visible.

*Performed on a General Electric recording spectrophotometer in the American Cyanamid Laboratories, Stamford, Connecticut.

TABLE 3. *Cold Agglutinins by Tube Method* at Different Temperatures.*

DATE	TITER AT 37°C.	TITER AT 26°C.	TITER AT 7°C.	TYPE OF CELLS	PATIENT'S SERUM
In hospital:					
4/9	1:5	1:1280	1:1280	Patient's (washed)	Fresh
	1:5	1:1280	1:1280	Type O	Fresh
4/18	1:5	1:5120	1:5120	Patient's (washed)	Inactivated
	1:5	1:5120	1:5120	Type O	Inactivated
	1:5	1:5120	1:5120	Patient's (washed)	Inactivated (complement added)
	1:5	1:5120	1:5120	Type O	Inactivated (complement added)
4/30	0	1:40	1:2560	Patient's (washed)	Inactivated
After discharge:					
6/8	0	Not done	1:80	Patient's (washed)	Inactivated
8/14	0	Not done	1:320	Patient's (washed)	Inactivated
9/27	0	0	1:160	Patient's (washed)	Inactivated

*Procedure consisted of serial dilutions of serum in physiologic saline solution beginning at 1:5. The total volume of serum in addition to physiologic saline solution was 0.5 cc. To each of the tubes 0.2 cc. of cell suspension was added. As indicated, Type O or adequately washed patient's cells were used. All tubes were incubated overnight, and then the agglutination was dispersed by incubation at 37°C. The serum titers are expressed independently of the further dilution produced by the volume of fluid in which the cells were suspended.

The spectral analyses of the serums are presented in Figure 2. The control specimen revealed a faint trace of absorption that seemed insignificant and possibly represented an unavoidable minimum of hemolysis. The 30-minute curve disclosed characteristic spectral absorption bands of oxyhemoglobin. The 45-minute specimen showed similar absorption bands differing only quantitatively from the preceding specimen. The 60-minute specimen demonstrated the absorption bands of the serum to be markedly reduced and only slightly greater than those of the control serum. This amount of residual hemoglobin seems significant only as showing a nearly complete cessation of the local hemolysis.

The spectral analyses of urine samples are presented in Figure 3. These are marked 0, 1½ hours and 12½ hours, respectively. None of these samples showed any trace of absorption bands in the zones of oxyhemoglobin. The absence of hemoglobinuria suggests that the systemic hemoglobinemia did not reach a sufficient concentration to appear in the urine and was disposed of by some other mechanism.

Within a few minutes after immersion, a peculiar dark-purple mottling of the immersed portion of the arm was noticed. Fifteen minutes after removal of the arm from the ice water, this began to disappear, and the skin resumed its normal appearance after 1 hour. The local mottling was thought to be due to reversible intravascular agglutination in the chilled skin and subcutaneous tissue, resulting in obstruction of the lumens of small vessels, which in turn gave rise to local, mottled cyanosis.

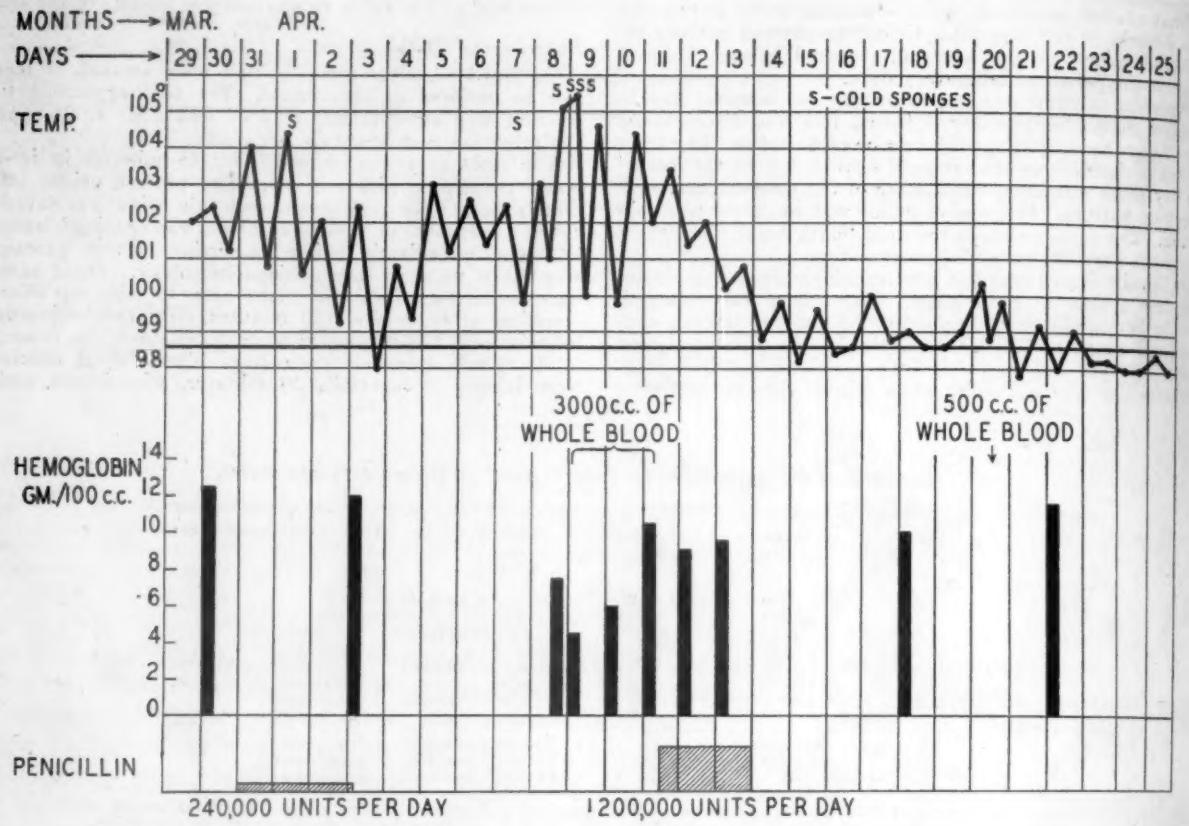
MONTHS → MAR. APR.
DAYS → 29 30 31 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
TEMP.
105° 104 103 102 101 100 99 98
S
S SSS
S-COLD SPONGES
3000 c.c. OF WHOLE BLOOD
500 c.c. OF WHOLE BLOOD
HEMOGLOBIN GM./100 c.c.
14 12 10 8 6 4 2 0
PENICILLIN
240,000 UNITS PER DAY
1200,000 UNITS PER DAY

FIGURE 1. *Temperature Chart, Hemoglobin Levels and Penicillin Therapy.*

TABLE 4. *Hemolysis* at Different Temperatures.*

DATE	TITER AT 37°C.	TITER AT 26°C.	TITER AT 7°C.	TYPE OF CELLS	PATIENT'S SERUM
In hospital:					
4/9	1:5	1:5	1:5	Type O	Fresh
	1:5	1:5	1:5	Patient's (washed)	Fresh
4/18†	1:10	1:10	1:10	Type O	Fresh
	1:10	1:10	1:10	Patient's (washed)	Fresh
	1:10	1:10	1:10	Type O	Inactivated
	1:10	1:10	1:10	Patient's (washed)	Inactivated
4/30	0	0	0	Patient's (washed)	Inactivated
After discharge:					
6/8	0	0	0	Patient's (washed)	Inactivated
8/14	1:10	1:10	1:10	Patient's (washed)	Inactivated

*No hemolysis was more than a slight trace. Except for the duplicate tests with guinea-pig complement, this table does not represent separate tests but merely shows hemolysis read in the cold-agglutinin tubes, independent of shaking.

†Duplicate sets of each test with 4 units of guinea-pig complement showed identical titers.

DISCUSSION

Cold agglutination of homologous and heterologous erythrocytes has been sporadically reported in

various diseases and much more regularly in association with primary atypical pneumonia. Occasionally, a hemolytic anemia develops in the course of primary atypical pneumonia associated with powerful cold agglutinins in the serum. Confusion of this type of hemolytic anemia with that associated with sulfonamide therapy has been dispelled by the recent report of a case in which no sulfonamide was given.[3] There seems to be little reason not to regard the acute hemolytic anemia of primary atypical pneumonia as a distinct entity due directly to the action of cold agglutinins on the red cells of the patient. Intravascular hemolysis by cold agglutinins depends on the trauma suffered by previously agglutinated erythrocytes in their passage through fine blood vessels. The degree of destruction of erythrocytes is proportional to the titer of the agglutinins and the heaviness of the cell suspension.

The production of hemolytic anemia seems to depend on many factors, such as the temperature

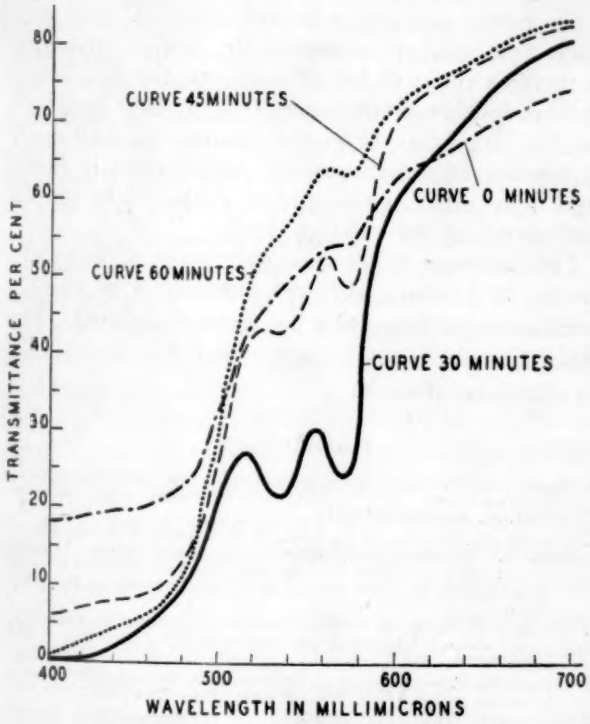

FIGURE 2. *Serum Absorption Bands following Chilling.*

of potent cold-agglutinin activity, the number of red cells destroyed and the duration of exposure. These are considered individually below.

The temperature factor cannot be divorced from the titer of the agglutinins because of their close inverse relation, as shown by other observers.[4, 6, 7] Since the exact cold-agglutinin titer for production of hemolysis in vivo is not known, for the sake of convenience in discussing the effect of temperature, an arbitrary term, "temperature hemolysis factor," is introduced. This is defined as the maximum tem-

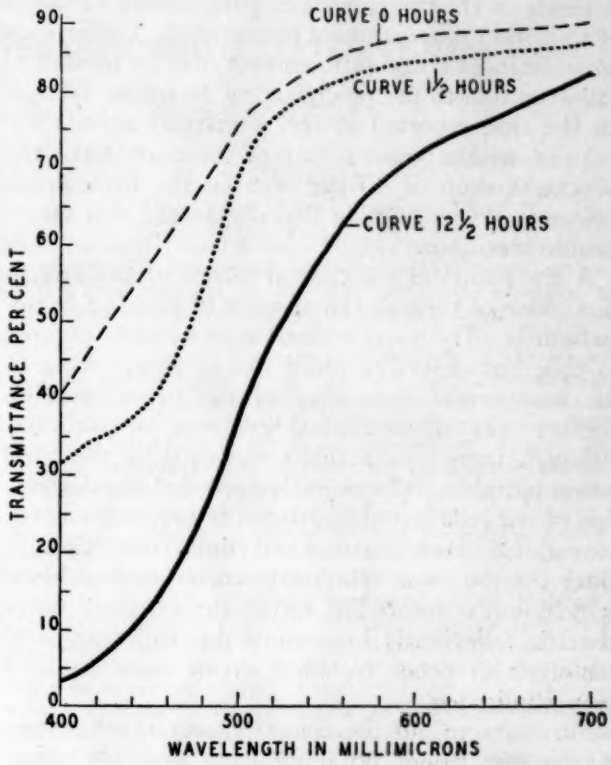

FIGURE 3. *Urine Absorption Bands following Chilling.*

perature at which cold agglutinins are sufficiently active to give intravascular hemolysis. This term is important, since cold agglutination, for the most part, is a phenomenon observed at refrigerator temperatures.*

The term "cold" is relative, and cold agglutination has been observed repeatedly at temperatures ranging from 20 to 37°C. These ranges coincide with skin temperatures under conditions of ordinary exposure. When the temperature hemolysis factor and skin temperature coincide, hemolysis must occur.

The temperature to which the skin must be lowered to give hemolysis is directly related to the temperature hemolysis factor of the cold agglutinins. Unusual chilling, as in the case presented above, may be necessary for hemolysis if the temperature hemolysis factor is low, but not necessarily if the factor is sufficiently high.

Mere hemolysis does not lead to anemia unless a sufficient quantity of erythrocytes are destroyed.

*In the experience of one of us (J. G. S.), 20 cases of elevated cold-agglutinin titers have been studied. The case presented above is the only one in which activity at 26°C. could be demonstrated and in which hemolytic anemia was present. The titers at 7°C. in these cases ranged from 1:160 to 1:5120 (expressed in terms of dilution of serum).

This quantity must be related to the volume of tissue exposed and the duration of exposure. We have no evidence on which to base any estimation of the proportionate, quantitative effect of these factors.

The production of acute hemolytic anemia thus depends on the coincidence of a number of variables of uncertain proportionate importance. Under such circumstances a dramatic episode may be needed to call attention to the precipitating factor or factors. In the case reported above, a marked anemia developed without much hint of its cause until the overnight drop of 40 per cent in the hemoglobin following severe chilling literally forced this factor to our attention.

A few points of the clinical record need clarification. One of these is the absence of proof of hemoglobinuria. The nurse's observations clearly pointed to this, but objective proof was lacking, owing to the inadvertent discarding of the urine samples. Neither was there clinical evidence of jaundice, although there was a slight elevation of the total serum bilirubin. The objective proof of the destruction of red cells rested largely on the red-cell counts, hemoglobin determinations and clinical observations. Since the counts in relation to corresponding blood hemoglobin contents fell within the expected range of error, fallaciously low counts due to intrapipette hemolysis or other technical errors seem to have been eliminated.

Furthermore, all the counts except the first two were mean values obtained from multiple determinations in which warm diluent, warm pipettes, shaken at incubator temperature, and warm hemocytometers were used to avoid such difficulties. The total change in the counts was too large and too rapid to be accounted for in any other way than by intravascular hemolysis or massive hemorrhage. There was nothing to suggest a hemorrhage of such magnitude.

To explain the absence of jaundice, the mode of disposal of the released hemoglobin is of prime importance. Destruction of the same number of red cells in other conditions usually results in marked bilirubinemia and clinical jaundice. We are forced to assume that a large portion of the hemoglobin was disposed of in the urine in this case. There appears to have been a difference between the mode of disposal of intravascularly released hemoglobin and the extravascular destruction of red cells. This hypothesis is under investigation. Intracellular hemosiderin granules in the cells of the urine sediment, in the absence of transfusion reaction, suggested renal disposal of the hemoglobin.

Summary

A case of primary atypical pneumonia in which potent cold agglutinins resulted in an acute hemolytic anemia in the absence of sulfonamide medication is presented. At the time of the development of maximum anemia, cold agglutination was present in the serum with identical titers at 25 and 7°C. At that time a trace of agglutination was even present at 37°C. The anemia developed coincidentally with the administration of cold alcohol sponges and exposure.

With recognition of the cause of hemolysis, further, and possibly fatal, hemolysis was prevented by rigid precautions against chilling, in spite of even higher titers of agglutinins found later in the disease.

A mechanism of local hemolysis was demonstrated experimentally, confirming the findings of Stats and his associates.

The temperature factor of the cold agglutinin activity is just as important as the level of cold agglutination at 7°C. The cold-agglutination test should be done routinely in triplicate racks incubated at 7, 26 and 37°C. Although an arbitrary level cannot be given, any appreciable titer of cold agglutinins at or above 26°C. should probably be considered potentially dangerous.

Acute hemolytic anemia due to the mechanism demonstrated should be avoidable.

Since cold sponges, administration of antipyretic drugs and ordinary exposure are routine procedures in the treatment of febrile patients, the significance of these factors in the production of acute hemolytic anemia in primary atypical pneumonia may easily be overlooked. Alertness to these factors in future cases may make it possible to evaluate the general application of the case reported.

This appears to be the only case of hemolytic anemia in primary atypical pneumonia in which a mechanism of hemolysis has been elucidated. This hypothesis is strongly supported by clinical and experimental data.

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PREFRONTAL LOBOTOMY IN THE CHRONIC DEPRESSIVE STATES OF OLD AGE

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THE operation known as prefrontal lobotomy was first performed by Moniz[1] in 1936. Since that time, the procedure has been widely employed in many types of mental illness in which the course of the disease has been prolonged and the outlook desperate. The operation consists of the cutting of a part of the fibers between the thalamus and prefrontal lobes.[2, 3] The rationale has been to dissociate, by surgical means, pathologic thinking from its emotional reverberation. This, of course, is a vast oversimplification of an extremely complex psychologic and neurophysiologic event. The results, when successful, have relieved patients of overwhelming anxiety, obsessive thinking, depression and other crippling emotional reactions. The best results have been obtained in chronic depressions and in some obsessive-compulsive states in which there is marked anxiety. It has been the experience of most observers that the results in chronic schizophrenia are far from satisfactory.

Mental illness in old age is usually regarded as a hopeless problem. The physician has an attitude of therapeutic nihilism and, as a rule, tends to classify all syndromes as organic and to emphasize the deteriorating aspects of senility. The realities of old age, as well as the lack of physical and mental resiliency, make most types of therapy extremely difficult, even when it is recognized that the essential features of the psychosis are those of a depression. It is a frequent clinical experience that such patients react poorly to electric shock therapy. For this reason, the following case histories of 4 women, over sixty years of age, with chronic depressions whose symptoms were greatly alleviated by means of prefrontal lobotomy are reported:

CASE 1. The patient was a 73-year-old woman whose family history was replete with mental illness. A daughter had recurrent manic-depressive episodes, a son had a severe anxiety state, and there was a strong familial history of mental illness in the patient's siblings and collateral relations. The family described her as a sensitive person who tended to worry over details. On the whole, however, she got along with her friends and showed no mental abnormalities until the age of 63. The depressive episodes, at first, lasted only a few months and usually occurred in the spring.

In 1944 the patient began to feel depressed in the winter, when she was first seen by us. She was quite depressed and extremely agitated, and hypochondriasis was marked. In April, 1945, she was sent to an institution, where she remained for several months without any improvement. Finally, her condition became so marked that she was given electric-shock treatment in October, despite her advanced age and in the presence of auricular fibrillations. She again received electric-shock therapy in November and December, without improvement.

Because of the pronounced agitation and intractable depression, a prefrontal lobotomy was performed on December 22 by Dr. James L. Poppen. Almost immediately, the patient's mood improved. There was some difficulty in control of the bladder for about 4 weeks. During the 3rd postoperative week, she was playing bridge. Subsequently, she was relaxed, and there was no recurrence of the depression or agitation. She carried on her household duties as before, and she was quite capable of meeting people adequately. There was no obvious change from the level of intellectual abilities that she had maintained prior to operation. So far as the family was concerned, there was no change in personality or temperament, and she was much more agreeable to live with than at any time in many years. When last seen, she was pleasant, courteous and alert and gave every evidence of being a reasonably content elderly woman who was aging in a satisfactory fashion.

CASE 2. This patient, a 62-year-old woman, had a sister who had been in a mental institution for many years because of a chronic depressed state. Throughout her life, the patient had had occasional episodes of depression, usually lasting several months at a time and associated with strong feelings of hopelessness and marked somatic disturbance. She was first seen in May, 1944, when she had been severely depressed for 10 months. She was given four electric-shock treatments, with partial recovery, and in October of the same year she was given five more. Subsequently, she did quite well for a year, when there was a recurrence of depression for which she received seven electric shocks. She showed only temporary improvement, and shortly thereafter the depression and agitation recurred. She was unable to sleep and lost considerable weight because she refused to eat.

In January, 1946, a prefrontal lobotomy was performed by Dr. Poppen. Almost immediately the patient became cheerful, and within several months she had gone back to managing her household. This improvement has continued until the present time. The husband stated that she had been uniformly happy and untroubled. When unusually tired she seemed quieter than formerly, but never depressed, and readily recovered from the fatigue. She was entirely capable of controlling the family budget, planning her work, shopping and so forth. She enjoyed meeting people — even pouring at a faculty tea. Her intellectual capacity was no different from that in the past. Friends told the husband that in the 20 years they had known the patient, she had never seemed so well and so normal. He could detect no personality

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changes except the absence of fear. Occasionally, she seemed somewhat detached and showed a slight loss of initiative, but these episodes were so slight as to be scarcely worthy of mention. The really significant thing was that she was able to meet greatly increased responsibilities better than for a long time.

CASE 3. A 67-year-old woman was first seen in January, 1942. Her family history was strongly positive for manic-depressive psychosis. A brother had committed suicide, and a sister had had several admissions to a state hospital. The patient had had at least six episodes of mental disease during the previous 10 years. The periods consisted of overactivity lasting several months, associated with euphoria, and were followed by periods of exhaustion, depression and loss of energy. As the years went on, the attacks became more prolonged, and the depression more pronounced. Freedom from symptoms was of brief duration. As in the other cases, there was no delusional formation, no sense of guilt and no retardation. Chiefly, there was a feeling of depression and an absence of energy, drive and interest.

During the next 4 years, the patient was seen during four episodes, in each of which the depressions were terminated by electric-shock treatment until the last attack, which remained intractable to shock therapy; the patient had no remission, remaining completely depressed for 7 months prior to prefrontal lobotomy.

The operation was performed in April, 1946, by Dr. Poppen. The patient's mood changed almost immediately, and she was subsequently pleasant and relaxed. There was no return of depression, but from time to time she complained of a sense of fatigue and weariness. It appears almost that the deep affective disturbance of depression had been altered by the operation in some manner, so that it was experienced as a considerably more endurable reaction. The patient met people well, and intellectually she seemed normal. On the whole, the operation was extremely successful.

CASE 4. A 53-year-old woman was first seen in 1937, when she had been depressed for over a year. There was a history of two previous episodes, the first occurring in the third decade, the other in the fifth. During these attacks, she was depressed, had marked insomnia and anorexia, lacked endurance and was extremely agitated. There were no delusions, feelings of guilt or paranoid trends. She was next seen in 1942. In the interval, she had been in a mental institution, where she was given electric-shock treatment. She improved for a short while, but rapidly slipped back into the previous condition. In 1946 the patient was seen again, and in view of the fact that the depression had lasted in an unmitigated fashion for 10 years despite electric-shock and other treatment, it was decided that prefrontal lobotomy was urgently indicated.

In July of that year, the operation was performed. The patient was quite confused for several weeks after the operation, but then began to show definite signs of improvement. Subsequently, she functioned at a much higher level than previously. She visited friends and did some shopping and entertaining at home for the first time in almost a decade. She herself stated that she had periods in which she felt rather low and lacked energy, but this was not obvious to her family, and in general she behaved in a more socially adequate fashion. There was no impairment of intelligence or judgment.

The cases described above have several features in common. First of all, the patients were all women in the declining years of life who had been mentally ill for years. Secondly, the clinical syndromes were similar. The outstanding features were depression, lack of energy and enthusiasm and retreat on the basis of an overwhelming disturbance in the affect of the patient. In none of these cases was there marked retardation of speech or strong suicidal drives, and paranoid or guilt reactions were not apparent. Thirdly, they all responded remarkably to prefrontal lobotomy. In each case there was a radical improvement both in the way the patient herself felt and in the manner in which she behaved. This resulted in a marked alleviation of the tension and distress that are pronounced in the depressed states. In no case was there obvious intellectual impairment. Of course, none of these women had led an intellectual life in the past, nor had they held positions of responsibility, but judging by past performances — the ultimate criterion — they behaved in a far more useful and socially adequate fashion after the operation. The operation in each case relieved the patient of depression in a striking manner. In at least 1 case, however, a definite sense of fatigue remained, possibly owing to the same factors that were responsible for the depression, but with the severance of the cortico-thalamic pathways, the process is experienced as fatigue rather than as a deeply lowered mood.

The point that is especially emphasized is that old people with chronic depressions should not be regarded as hopeless and doomed to live out their remaining years in retreat and unhappiness. Properly performed, prefrontal lobotomy can do them no harm. We have, as yet, experienced no failures, and it should be emphasized that only cases in which at least a year had elapsed since the operation are reported. The alternative to the operation is to add the misery of melancholia to the disabilities of old age.

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MALIGNANT TESTICULAR NEOPLASMS IN INFANCY*

Report of a Case with Six-Year Survival

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MALIGNANT tumors of the testicle in children are rare. Dargeon,[1] reviewing malignant tumors in 1557 children collected from five major sources, found 211 cases involving the genitourinary tract. Matassarin[2] quotes Gilbert, who collected 5500 cases of all tumors of the testicle reported in detail from 1803 to 1942 and observed only 131 cases in children under fifteen years of age.

There are several reports of testicular neoplasm in children in the early literature.[3, 4] These have been responsible for the frequently quoted opinion that "there have been numerous reports of malignant tumors, usually teratomas in the newborn."[5] Wells,[6] however, in a classic article on congenital malignant neoplasms, pointed to the lack of actual proof that the testicle is the seat of congenital cancer. He mentioned several doubtful cases from the early literature and concluded as follows:

> No more recent reports [after 1900] can be found indicating congenital or even early infantile malignant growth in the testicle, which makes all earlier reports even more doubtful. . . . Of 100 malignant testicular tumors reviewed by Tanner (1922) only one occurred before the seventeenth year. In a review of malignant disease of the testicle Dew (1926) mentioned only two cases in infants.

It is worthy of note that only four histologic reports of malignant testicular tumors in infants could be found. Two of these are cited by Wells,[6] as follows:

> A typical case is that of Philipp, in which the testicle was enlarged at birth. Not until traumatized in the third year did it grow rapidly, and on removal, sarcomatous degeneration of a growth, diagnosed as teratoma, was found. MacLennan also reported a case in which enlargement of the testicle was present at birth, with resection at the eleventh month, followed by development of metastases in abdominal and cervical glands, and death in two weeks. Histologically it was considered to be adenocarcinoma.

The recent literature provided two additional case reports, one of which describes a seven-month-old infant with enlargement of the left testicle noted one month prior to treatment.[2] The patient was treated by simple orchidectomy and postoperative radiation and was reported living and well after a follow-up study of four and a half months. The diagnosis was embryonal adenocarcinoma. Another case was noted three days after birth in the right testicle.[7] Orchidectomy was performed, and a diagnosis of Wolffian epithelioma was made. The authors report the case as unique in the literature of Argentina. The diagnosis in the last case might well correspond with that of the two preceding cases.

The following case of adenocarcinoma of the testis is considered worthy of report because of the rarity of the neoplasm so early in infancy and because of the long follow-up period with apparent cure:

A. S. (B.I.H. 54467), an 8-month-old boy, was admitted to the hospital on September 4, 1940, because of a swelling of the right testicle. The infant had been born after a full-term normal delivery. At birth the child showed no signs of injury and weighed 9 pounds. At an early age the scrotum was noted to be somewhat larger than normal, but both testicles were felt to be of normal size within the scrotum. An attempt was made, at the time of the first visit to the Tumor Clinic on October 8, to obtain specific information on this point. The mother stated that she had noted an

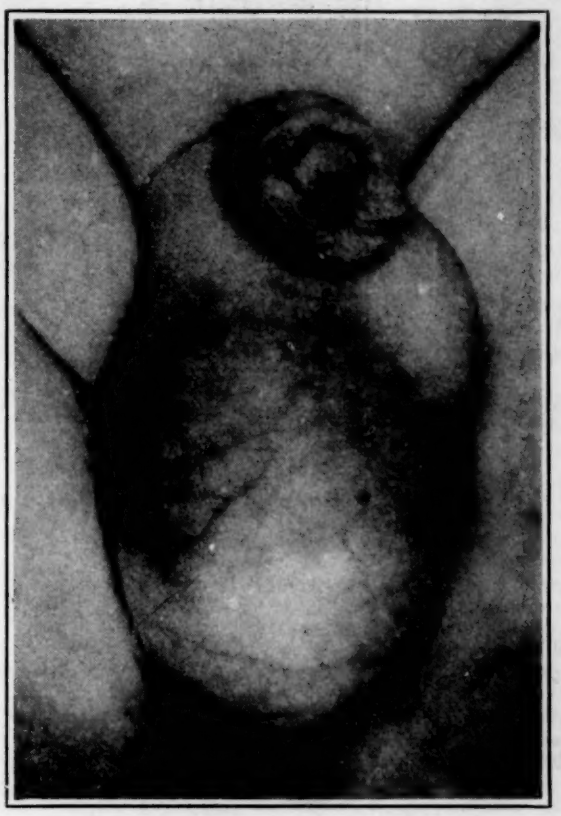

FIGURE 1. *Photograph of the Scrotum on Admission.*

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enlargement in the scrotum immediately after the child's birth. This was pointed out to the family physician during the course of an examination at the age of 1 month, but he did not consider that there was anything abnormal in the scrotum. At 4 months a mass was noted in the scrotum. A physician was consulted at that time and called it a hydrocele, deciding that no treatment was indicated. Since a brother of the patient had had a similar swelling, which had been called a hydrocele and disappeared at the age of 15 months, the mother had accepted this advice with confidence and had not hastened to consult a physician again. The swelling of the right testicle felt alternately hard and soft but was never reducible. It had not grown much in size since it had first been noted but had become consistently harder. The child had gained normally in weight, the weight on admission being 23 pounds. No signs other than the scrotal mass had been noted. On August 30 the mother had again consulted a physician, who had advised admission to a hospital.

Physical examination revealed a chubby, somewhat pale child. The skin was normal. Abdominal examination revealed no masses. No inguinal lymphadenopathy was noted. The penis had been circumcized. The scrotum was considerably enlarged and tense (Fig. 1), but the overlying skin was not reddened, edematous or warm. Palpation revealed the left testicle to be normal in size and consistence. It was pushed far over to the left by a large mass in the region of the right testicle. The right testicle could not be discerned. In the right side of the scrotum there was an egg-shaped mass measuring about 6 cm. in its greatest diameter. The mass seemed tense rather than hard in consistence. Its surface was smooth. There were no masses in the inguinal canal. The mass did not transilluminate light. No impulse was transmitted when the child cried or coughed. The overlying skin was freely movable. The mass could not be reduced or displaced toward the inguinal region. The perineum was normal. Rectal examination was not done.

Examination of the blood disclosed a red-cell count of 4,640,000, with a hemoglobin of 80 per cent, and a white-cell count of 7400, with a normal differential count. Examination of the urinary sediment revealed occasional white cells, and 1 or 2 red cells per high-power field, but no casts. The Aschheim–Zondek test was negative.

X-ray examination of the lungs was negative. There was no evidence of metastatic lesions in the shoulders, ribs, dorsolumbar spine, pelvis and hips. X-ray study of the scrotum revealed a large soft-tissue mass in the right testicular region in which no calcification was noted.

On September 12 a right orchidectomy was performed, with ligation and transection of the spermatic cord at the level of the external inguinal ring. No hydrocele was present.

Gross pathological examination disclosed that the tumor weighed 49 gm. and measured 5.5 by 4.5 by 4.0 cm. (Fig. 2). It appeared completely encapsulated by reddish-tan fibrous tissue. The tumor mass occupied most of the submitted specimen, and was covered by a thin, glistening tan membrane. There was no gross evidence of remaining testicular tissue. The cut surface of the tumor presented a variegated appearance. Most of the tissue was a brilliant yellowish brown, but it was mottled by reddish-brown hemorrhagic areas and by red necrotic patches. The tumor tissue bulged above the cut edge of the capsule and was edematous; it was soft in consistence, but not uniformly so. Numerous small cystic areas filled with a colorless gelatinous material were seen, but the cut surface as a whole had a gelatinous texture.

FIGURE 2. *Photograph of the Tumor on Section, Showing Gelatinous Appearance and Areas of Hemorrhage, Necrosis and Cystic Change.*

Microscopical examination of six sections revealed an essentially uniform picture of a neoplasm that was pleomorphic and undifferentiated. The neoplastic cells were variable in shape, size and staining reaction. The predominant cell type was characterized by a large, round, vesicular nucleus containing coarse clumps of chromatin; this type of nucleus was surrounded by pale-staining cytoplasm that frequently exhibited vacuolization. The other neoplastic cells were anaplastic variations of this predominant cell type. The neoplastic cells grew in the form of masses, cords and strands; abortive acinus formation was also present in some areas. The cells forming the abortive acini were hyperchromatic. Numerous mitotic figures were found among the neoplastic cells. The stroma of the tumor itself varied from scanty and tenuous to abundant and dense in different areas.

In the areas where it was scanty the stroma appeared loose, wavy and myxomatous, and the neoplastic cells were well preserved. In other areas the stroma was necrotic and contained degenerating neoplastic cells. In a few places complete necrosis to acidophilic amorphous debris was present. A few focal hemorrhagic areas were also encountered. Necrosis and hemorrhage were less frequent in the compact cellular areas of neoplastic tissue where the cells were fairly well preserved and where attempted acinus formation was present. The tumor was surrounded by a thick fibrous capsule, which contained remnants of both flattened and well preserved seminiferous tubules. The capsule was slightly invaded by neoplastic cells, and these areas of invasion exhibited infiltration by chronic inflammatory cells at the growing edge of the tumor. The large vacuolated cells seen in the tumor suggested embryoma, but the attempted acinus formation suggested carcinoma of the testis. The diagnosis was adenocarcinoma of the right testis.

The postoperative course was uneventful. Healing occurred by primary union, and the patient was discharged on the 12th postoperative day in excellent condition.

The patient was followed in both the Tumor Clinic and the Genitourinary Clinic. Radiation therapy was not given. The child developed normally, both physically and mentally. Five months postoperatively examination revealed several firm, discrete, freely movable lymph nodes in the right groin, and a few smaller ones in the left. This was considered to be secondary to mild penile irritation. In January, 1942, and again in January, 1947, x-ray study of the chest disclosed no evidence of metastatic disease. Intravenous pyelography on the latter occasion was likewise negative. The child was alive and well when last seen in January, 1947. It was noted that the inguinal lymph nodes had not changed in size during a 6-year period of observation. He appeared to be somewhat smaller than other children of his age, although x-ray studies of the long and flat bones revealed no retardation in bony growth.

Summary

A case of malignant testicular tumor in an infant is reported. This appears to be one of the few authenticated case reports of malignant testicular neoplasm occurring in the early months of infancy. Another interesting feature of this case is the six-year survival period, with apparent cure. For a tumor characterized by such a high grade of malignancy and rapid growth in the first years of life, this long survival period is noteworthy. It represents the only reported five-year survival of an infant with a malignant testicular neoplasm.

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MEDICAL PROGRESS

SERUM LIPIDS AND THEIR VALUE IN DIAGNOSIS*

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THE serum and the lymph fluid not only are the transport medium for all substances absorbed in the intestines but also contain substances that have originated as a result of intermediary and cellular metabolism. It may therefore be assumed that lipids found in the cells of the organs should also be present in the serum. Such an assumption corresponds only partly with the actual analytical findings. The concentration of certain lipids, although fairly high in the cells of organs, is so low in the serum, and the amount at the disposal of chemists working in the clinical laboratory so small, that present methods are not sensitive enough for their determination.

The lipids important for human physiology and pathology are classified as follows[1]:

Neutral fat: glycerol esters of various saturated and unsaturated fatty acids.

Monoaminophosphatides: fatty acid esters of a phosphorylated polyvalent alcohol, combined with a nitrogen-containing group. Their phosphorus-nitrogen ratio is 1:1. (Some monoaminophosphatides contain other organic groups in addition to those already mentioned.)

Lecithins: phosphoric acid diesters of diglycerides and choline.

Lysolecithins: phosphoric acid diesters of saturated monoglycerides and choline.

Cephalins: contain their total nitrogen in form of a primary amino group (ethanolamine or serine).

Phosphatidyl ethanolamines: phosphoric acid diesters of diglyceride and ethanolamine.

Phosphatidyl serines: hydrolysis products — fatty acids, phosphoric acid, polyvalent alcohols, serine.

Plasmalogens (acetalphosphatides): phosphoric acid diesters of a higher fatty aldehyde acetal of glycerol and of ethanolamine.

Inositol phosphatides: obtained from brain, soybeans and bacteria.

Phosphatidic acids (cardiolipins): hydrolysis products — fatty acids, polyvalent alcohols, phosphoric acids (bound as a monoester).

Phosphatides of acid-fast bacteria: hydrolysis products — phosphoric acids, polyhydroxyl compounds (such as inositol), fatty acids with straight and branched chains.

Diaminophosphatides (sphingomyelins): acid amide of sphingosine with fatty acids (ceramides) in ester linkage with phosphorylcholine.

Cerebrosides: acid amides of fatty acids with sphingosine or dihydrosphingosine in glucosidic linkage with galactose or glucose.

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Sulfuric acid esters: derived from cerebrosides.
Gangliosides: structure unknown; hydrolysis products — sphingosine, neuraminic acid, fatty acids and galactose or glucose.
Sterols:

Cholesterol and its esters derived from animal tissues.
Cholesterol and its esters derived from plants.
Hydrocholesterols.
Vitamin D.
Steroid sex hormones.
Bile acids.

To facilitate an understanding of the roles of the lipids in human disease it appears necessary to discuss the clinical physiology of lipid metabolism.

* * *

Neutral Fat

Hyperlipemia — that is, the increase of neutral fat in the serum — is visible to the naked eye because the serum loses its transparency and becomes milky or even creamy in appearance. It should be emphasized that an increase of cholesterol or phospholipids without an increase of neutral fat never causes a milky serum. The designation "hyperlipemia" should be exclusively reserved for an abnormal increase of neutral fat in the serum, whereas the terms "hyperlecithemia" and "hypercholesterolemia" should be used to designate the increase of these respective lipids in the serum. Hyperlipemia is usually accompanied by hypercholesterolemia and hyperlecithemia, whereas hypercholesteremia and hyperlecithemia occur without hyperlipemia in essential xanthomatosis of the hypercholesteremic type, as well as in xanthomatous biliary cirrhosis, as pointed out below.

Postprandial Hyperlipemia

This is a physiologic occurrence after the intake of a fatty meal. The peak is observed within three to five hours. Formerly, it was erroneously believed that hyperlipemia is found in obese people. On occasions postprandial hyperlipemia may persist for an unusually long period in obese persons. If the serum is examined in the postabsorptive state, however, there is no hyperlipemia. It should be emphasized that for the routine analysis of blood for neutral fat, the patient should always be examined in a fasting state.

Retention Hyperlipemia

Hyperlipemia may be caused by a sluggish removal of neutral fat from the blood stream into the fat depots and into the organs that metabolize fat. The mechanism of such a disorder is not clear at present. It may be a neuroregulatory dysfunction or an anatomic change in the wall of the capillaries from which the neutral fat passes into the tissue spaces. This form of retention hyperlipemia is relatively rare, and its clinical designation is "idiopathic hyperlipemia." It may occur as an inherited disorder,[2–5] or it may occasionally be observed in single cases with and without secondary eruptions of skin xanthomas. The lipid partition in a typical case is given in Table 1. Since slight glycosuria is present in some cases, the diabetes was formerly considered the causative factor of the hyperlipemia. In these cases, however, the hyperlipemia, as well as the glycosuria, disappears after the patient has been given a diet low in neutral fat.[5a] Insulin in these cases has no effect on the hyperlipemia. Idiopathic hyperlipemia with hepatosplenomegaly and secondary xanthomatosis of the Bürger–Grütz type also probably belong to this group.[6, 7]

Table 1. *Lipid Partition of Serums and Liver in a Case of Idiopathic Hyperlipemia.*[9]

Lipid	Range for Normal Liver	Liver in Idiopathic Hyperlipemia	Range for Normal Serum	Serum in Idiopathic Hyperlipemia
	gm./100 gm.	*gm./100 gm.*	*mg./100 gm.*	*mg./100 gm.*
Total cholesterol	2.1 - 2.6	2.52	150–260	379
Free cholesterol	0.44– 0.55	0.73	40– 70	158
Cholesterol esters	1.50– 2.15	1.79	70– 75*	60*
Total phospholipid	9.0 –11.0	10.05	150–250	465
Sphingomyelin	0.3 - 0.5	1.44	10– 30	13
Cephalin	3.0 - 5.5	3.05	0– 30	Traces
Lecithin	3.0 - 6.0	5.56	100–200	452
Total fatty acid	8.6 –13.0	9.45	200–450	3115
Neutral fat†	1.4 - 4.0	1.22	0–150	2740

*Percentage of total cholesterol.
†In idiopathic hyperlipemia the neutral fat is extremely high in the serum but in the range of normal in the liver.

Transportation Hyperlipemia

Hyperlipemia may occur as the result of an increased rate of transportation from the fat depots to the tissues. The classic example of this type of transportation hyperlipemia is observed in untreated, severe diabetes mellitus. The hyperlipemia in untreated severe diabetes disappears with insulin treatment but does not respond to a diet low in neutral fat. It is essential to distinguish patients with severe diabetes and transportation hyperlipemia[8] from those with idiopathic hyperlipemia and slight diabetes, because of the difference in

treatment. The former are severely sick, and in the latter, who seem to be healthy, the hyperlipemia is accidentally observed because of acute xanthomatous eruptions. The hyperlipemia observed in chronic pancreatitis,[10–12] as well as in glycogen-storage disease (von Gierke's disease),[13–15] is also considered to be the result of an increased rate of transportation from the fat depots to the organs that metabolize fats.

The mechanism of hyperlipemia and hypercholesterolemia observed in nephrotic conditions, such as lipid nephrosis, the nephrotic state of glomerulonephritis and renal-vein thrombosis, is at present not definitely clarified. It may be assumed that an increased rate of fat transportation also plays a part in these conditions.[16–18]

Phosphatides

The functions of the phosphatides in the organism, so far as they are known, may be distinguished as those pertaining to the intracellular metabolism and those playing a part in the transport of fatty acids. The monoaminophosphatides important for the transport of fatty acids are the lecithins, whereas the cephalins and sphingomyelins are found and retained mainly within the cells. The concentration of the latter in the serum is therefore low. In determining the total phospholipids of the serum 70 to 90 per cent may therefore be evaluated as lecithin. The significance of the lecithins in the transportation of fatty acids was shown by Sinclair and his co-workers[19–22] and by Artom and his associates.[23, 24] An intermediary of lecithin metabolism, glycerylphosphorylcholine, was isolated by Schmidt, Hershman and Thannhauser.[25] The occurrence of this substance in the intestinal mucosa provides a simple explanation for the rapid incorporation of ingested fatty acids into the phosphatide fraction.[19–22] The formation of glycerylphosphorylcholine from lecithin is effected by the action of a specific intracellular enzyme, lecitholipase.[25]

The liver is the main organ for phospholipid synthesis. Fishler, Entenman and Chaikoff,[26] using radioactive phosphorus, furnished strong evidence that the liver is the main site of plasma phospholipid (lecithin) formation. Hepatectomized dogs, receiving radioactive sodium phosphate intraperitoneally, showed only minute amounts of radioactive plasma phospholipids six hours after its injection, in contrast to control animals. Despite their reduced ability to form plasma phosphatides (lecithin), the hepatectomized animals were capable of synthesizing phosphatides at a normal rate in the kidneys and intestines.

Choline and cholamine are present in the monoaminophosphatide molecule. The lipotropic effect of choline and its precursors on the fatty livers of choline-deficient rats and of depancreatized animals has been demonstrated by various authors.[27–29] The amounts of phospholipids, especially those containing choline, are considerably reduced in choline-deficient rats.

It is, however, not proved whether choline or its precursors, the phospholipids, have any curative effect on fatty livers of heterogeneous etiology in human beings. The results of experiments on rats are not necessarily in conformity with bedside experience. The concentration of phospholipids in the serum is not diminished in patients with fatty livers from various causes.

The acetalphosphatides were first discovered by Feulgen[30, 31] in the cytoplasm of cells of all tissues and designated as plasmalogens. Although their function is unknown, their structural relation to cephalin gives a hint of their significance in the intracellular metabolism. No attempts have been made to isolate and determine this group of substances in the serum of human beings.

The concentration of cephalins and sphingomyelins in the serum, in contrast to the lecithins, is low and varies only slightly in healthy persons. These lipids are metabolized mainly within the cells, where they are formed. If changes occur in the total phospholipid concentration in the serum, they should be evaluated for their lecithin component.

In Niemann–Pick disease the concentration of sphingomyelin increases enormously in all organs with the exception of the brain. The serum of patients with Niemann–Pick disease, however, does not contain more sphingomyelin than that of normal subjects. The sphingomyelin is apparently retained in the cells where it is formed.[32–34] An analysis of the lipid content of the organs, serum and ascitic fluid in Niemann–Pick disease is presented in Table 2.

Cerebrosides

The cerebrosides are intracellular lipids. These substances are found in substantial quantities in normal brain tissue, where they are present as galactosidocerebrosides ranging from 4.0 to 6.0 per cent of dried tissue. The amount of cerebrosides in normal visceral organs is minute (0.1 to 0.6 per cent). Klenk[36] reported galactosidocerebrosides, as well as glucosidocerebrosides, in normal visceral organs. Both substances are determined quantitatively by the method of Ottenstein, Schmidt and Thannhauser,[37] in which small but measurable quantities of galactosidocerebrosides are found in normal visceral organs, whereas glucosidocerebrosides are found only in traces.

Carter, working on the lipid fraction of several hundred liters of serum provided by the plasma studies of Cohn and his group during the war, was able to isolate and identify minute amounts (approximately 100 mg.) of cerebrosides from 200 liters of plasma.[38] That these substances cannot be detected in 10 to 50 cc. of serum available for clinical determination is therefore not surprising. For practical

purposes the serum may be considered as lacking cerebrosides in determinable quantities.[37, 39] The cerebrosides are built and metabolized within the cells where they are encountered. In contrast to serum, normal red cells show cerebrosides in measurable amounts. Dried red cells contain 0.2 per cent, consisting entirely of galactosidocerebrosides.[37]

In Gaucher's disease the cerebrosides are accumulated in reticulum cells and histiocytes of the spleen, liver, lymph nodes and bone marrow (4 to 20 per cent). In contrast to the organs, the serum of patients with Gaucher's disease, like that of normal subjects, does not contain measurable quantities of cerebrosides,[37] and the concentration of cerebrosides in the red cells is not elevated above normal. For these reasons the analysis of serum and red cells for cerebrosides cannot be used for diagnostic purposes in Gaucher's disease.

Aghion[40] and Halliday and his co-workers[41] found that the cerebrosides that are accumulated in the visceral organs of patients with Gaucher's disease are not, as was formerly believed, galactosidocerebrosides but consist entirely of glucosidocerebrosides. In 3 cases of Gaucher's disease examined in our laboratory, 2 showed only glucosidocerebrosides, 8.3 and 11.3 per cent respectively, and 1 contained 7.2 per cent glucosidocerebrosides and 8.6 per cent galactosidocerebrosides.[37] In the infantile form of Gaucher's disease, in contrast to the adult form, only the galactoside variety of cerebrosides is found in increased concentration in the organs.[42] Up to the present only this one case of infantile Gaucher's disease has been examined for the variety of cerebrosides.*

Cholesterol and Its Esters

One should consider three different possibilities for the etiology of cholesterosis in cells and tissues: cholesterol infiltration into the cell, a process that results from an accumulation of cholesterol and cholesterol esters in the serum (hypercholesteremia); cholesterol accumulation and retention within the cell, which may originate from an increased synthesis and retention of cholesterol in the cell itself — this process is effected without increased supply of cholesterol and cholesterol esters from the blood stream; and extracellular precipitation or crystallization of cholesterol, which may be observed within the inflamed wall of the gall bladder or the degenerating wall of an arteriosclerotic vessel, which may occur without an increase of cholesterol in the serum and which is due to degenerative changes of the surrounding medium altering the physicochemical state of substances that are not in ionized solution in bile or serum, like cholesterol and part of the calcium.

The first and the second mechanism may result in xanthoma-cell (foam-cell) formation characteristic of the various types of xanthomatoses.

Thannhauser and Magendantz[43] and Thannhauser[44] classified the xanthomatous disorders according to the laboratory findings in the serum of these patients. The figures resulting from the quantitative analysis of lipids in serum are characteristic of three different groups of xanthomatous disease and hence of great value for their differential diagnosis.

Table 2. *Lipid Partition of the Organs, Serum and Ascitic Fluid in Niemann-Pick Disease.*[35]

Lipid	Spleen in Niemann-Pick Disease	Normal Spleen	Kidney in Niemann-Pick Disease	Normal Kidney	Liver in Niemann-Pick Disease
	% of dried tissue	*% of dried tissue*	*% of dried tissue*	*% of dried tissue*	*% of dried tissue*
Total cholesterol	6.73	1.8- 2.4	2.82	1.4- 2.8	7.00
Free cholesterol	6.70	1.0- 1.1	2.81	1.0- 1.1	4.50
Cholesterol esters	0.03	0.7- 1.3	0.01	0.5- 1.7	2.50
Total phospholipid	42.50	5.5-11.0	41.50	7.0-10.0	37.10
Sphingomyelin	32.70	0.7- 1.0	9.35	0.6- 0.8	25.90
Saponifiable phospholipid	—	—	—	—	—
(Cephalin)	—	—	—	—	—
(Lecithin)	—	—	—	—	—
Total fatty acid	—	—	—	—	—
Neutral fat	—	—	—	—	—
Cerebrosides	—	—	—	—	—

A high serum cholesterol, a normal cholesterol-cholesterol ester ratio, a moderately increased lecithin in the serum but a normal serum value for neutral fat (serum is transparent) are found in essential xanthomatosis of the hypercholesteremic type (hypercholesteremic familial xanthomatosis). Characteristic of this group are tuberous or plain xanthomas of the skin (similar to yellow carotene in color), xanthomas of tendons, atheroma formation in the intima of blood vessels and of the endocardial lining of the heart and xanthomas of the lining of bile ducts.

Normal cholesterol, lecithin and neutral-fat values of serum are observed in essential xanthomatosis of the normocholesteremic type (normocholesteremic xanthomatosis — synonymous with eosinophilic granuloma, Schüller–Christian syndrome and eosinophilic xanthomatous granuloma). The organs involved in this syndrome — singly, in various

*In the meantime examination of the organs of the patient's brother showed glucosidocerebrosides and galactosidocerebrosides.

combinations or generalized — are the skin (disseminata type of skin xanthoma), osseous system, dura, brain, lungs, pleura, lymph nodes and spleen. Enormously increased values of neutral fat (milky or creamy serum) but only moderately increased values of cholesterol and lecithin are characteristic of idiopathic hyperlipemia with secondary eruptive xanthomas and of related syndromes in which severe hyperlipemia is the primary cause. Parallel with the degree of hyperlipemia, inflammatory skin xanthomas appear and disappear. In visceral organs only a few scattered foam cells may be found.

Hypercholesteremia and Xanthoma Formation

The concentration of cholesterol in the serum seems to depend on many factors. Some of the possible causes of hypercholesteremia and xanthoma formation are discussed below.

Diminished destruction. Thus far, no enzyme capable of splitting the terpen-like ring of cholesterol has been isolated from mammalian tissues. The chemical changes that occur in the intermediary metabolism of the cholesterol molecule take place in the side chain of that molecule, such as esterification of the alcoholic hydroxyl group, hydrogenation and oxidation of the sterol ring as well as of the side chain. It is not definitely known whether the sterol sex hormones are metabolites of cholesterol or the result of sterol synthesis, notwithstanding the fact that pregnanediol glycuronitate containing deuterium was isolated from the urine of a pregnant woman after feeding of deuterium containing cholesterol.[45] Cholesterol derivatives in minimal quantities have been isolated from animal organs. It was suggested that cholestenone was present in deposits of cholesterol in the arterial wall.[46, 47] Hydrocholesterol has been isolated from the liver and from the serum of pregnant mares.[48] Dicholesterylether is present in the spinal cord of the ox.[49] Cholestenone is produced by the action of proactinomyces on cholesterol.[50]

A destruction of the cholesterol skeleton was concluded from negative cholesterol balance experiments.[51–56] In these experiments cholesterol was determined as cholesterol-digitonid. From the fact that the expected amount of cholesterol did not precipitate with digitonin it cannot be concluded that the cholesterol skeleton was destroyed in the intermediary metabolism. The sterol nucleus may well have been intact, whereas oxidative or reductive changes may have resulted in a sterol unprecipitable with digitonin or not giving the Liebermann–Burchard test. Since it has been shown that bacteria present in the intestinal tract transform cholesterol to a sterol not precipitable by digitonin,[57, 58] it may be concluded that the deficit of cholesterol in balance experiments in animals, as well as in man, is due to a bacterial action on cholesterol in the intestines rather than to a disintegration of the sterol ring in the intermediary metabolism. On the basis of present knowledge an accumulation of cholesterol in the blood serum or in the tissues cannot be explained by a diminished destruction of the sterol ring in the intermediary metabolism.

TABLE 2 (*Continued*).

LIPID	NORMAL LIVER	BRAIN IN NIEMANN-PICK DISEASE	NORMAL BRAIN	SERUM IN NIEMANN-PICK DISEASE	NORMAL SERUM	ASCITIC FLUID
	% of dried tissue	*% of dried tissue*	*% of dried tissue*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*
Total cholesterol	2.0- 2.6	6.45	7.3-15.0	196	150-260	73
Free cholesterol	0.4- 0.5	5.43	1.3- 4.6	41	40- 70	17
Cholesterol esters	1.5- 2.2	1.02	6.1-10.3	62*	70- 75*	56*
Total phospholipid	9.0-11.0	61.00	25.0-35.0	278	150-250	90
Sphingomyelin	0.3- 0.5	4.84	4.5- 7.0	24	10- 30	—
Saponifiable phospholipid	—	—	—	254	110-230	90
(Cephalin)	—	—	—	(8)	—	(34.7)
(Lecithin)	—	—	—	(246)	—	(55.3)
Total fatty acid	—	—	—	614	200-450	130
Neutral fat	—	—	—	322	0-150	82
Cerebrosides	—	—	—	0	0	—

*Percentage of total cholesterol.

Increased formation. As stated above, enzymes capable of splitting the sterol skeleton are not known to be active in the intermediary and cellular metabolism of animals. Consequently, an accumulation of cholesterol due to an intracellular enzymatic disturbance is not likely to be the result of a decreased cholesterol catabolism but rather of an increased anabolism — that is, increased synthesis of cholesterol. Earlier investigations of cholesterol metabolism have shown that the sterol-ring system is constantly synthesized in the mammalian organism.[53, 59–61] Schoenheimer,[62] by the administration of materials containing deuterium, demonstrated that the small molecules of two and three carbon atoms, which may be derived from all three food constituents (protein, carbohydrates and fats) are the basis of cellular sterol synthesis. Macleod and Smedley-MacLean[63] had already shown in 1938, by the use of acetic acid labeled with deuterium, that yeast is able to synthesize more than 50 per cent of its cholesterol from acetic acid. Bloch,[64, 65] in 1942,

employing labeled acetic acid in experiments with rat-liver slices, also demonstrated that considerable quantities of cholesterol are synthesized from acetic acid in the liver. The question that arises is, Which organs and cells are capable of cholesterol synthesis? Even if there is no definite answer, it is probable that every growing cell during maturation is capable of synthesizing cholesterol. This function in later life seems to be maintained in rapidly proliferating histiocytes and reticulum cells in certain disorders in which the functional capacities of embryonal cells — especially embryonal fat cells — to form all kinds of lipids are apparently preserved.[66, 67] In the fully developed organism the liver apparently plays a special part not only in the excretion but also in the synthesis of sterols. The experiments of Thannhauser, Enderlen and Jenke[68] on dogs with bile fistulas demonstrated that the synthesis of the sterol skeleton of bile acids occurs as a biologic synthesis in the liver. In further experiments it was shown that after liver extirpation in dogs the serum cholesterol is not considerably decreased after twenty-four hours.[69] The lowest cholesterol values, however, are observed in the serum of patients with acute yellow atrophy of the liver.[70] This observation supports the theory that the liver plays an important role in the formation of cholesterol in the mature organism. Different clinical manifestations may occur whether the increase of cholesterol formation takes place in or outside the liver. It may be suggested that the clinical syndrome designated by Thannhauser and Magendantz[43] as "primary essential xanthomatosis of the hypercholesteremic type" — with hypercholesteremia, hyperlecithemia but normal neutral fat content of the serum as the leading clinical signs — is the result of increased cholesterol and lecithin formation in the organism, possibly in the liver. The exact site of the increased formation of cholesterol, however, has not yet been ascertained.

This syndrome (hypercholesteremic familial xanthomatosis) is characterized by xanthoma formation in the skin (plain and tuberous xanthomas), xanthomas of the tendons, in which the nodules consist of cholesterol-containing foam cells and fibrous tissue, and xanthoma of the intima of the blood vessels and of the endocardial lining of the heart. The incidence of this syndrome in families as a recessive hereditary stigma is of great interest. The complete syndrome may be present in members of the same family, whereas in others only hypercholesteremia may be found — the incomplete form or *forme fruste*.[43, 71, 72]

Increased formation in the liver and impaired excretion. An imbalance of cholesterol formation and excretion is suggested as the cause of xanthomatous biliary cirrhosis, a syndrome that is characterized by the following clinical symptoms: skin xanthomas of the plain and tuberous variety, enlarged liver and spleen, obstructive type of jaundice of years' duration, extremely high values for total cholesterol (increased four to six times normal) and extremely high values for lecithin (increased four to eight times normal), transparent serum and diminished values for neutral fat in the serum despite the outstanding increase of cholesterol and lecithin.[43, 73–76]

On the basis of newer anatomic observations Thannhauser[73] has reconsidered his previous opinions concerning xanthomatous biliary cirrhosis and now suggests that the imbalance of cholesterol and lecithin formation and excretion is at the outset a functional disturbance of the liver.[77] In later phases anatomic changes in the bile capillaries (cholangioles) lead to a special type of biliary cirrhosis.* MacMahon and Thannhauser,[78] in a study of the livers of 5 patients showing the typical clinical signs of xanthomatous biliary cirrhosis, as described above, found in the early stages a nonspecific chronic inflammatory reaction centered about the smallest bile ducts and junction ducts of the portal areas. There was blocking of the ducts and subsequent intralobular bile stasis. The larger bile ducts were patent and free.

Xanthomatous biliary cirrhosis is an independent clinical syndrome, occurring together with plain and tuberous xanthomas of the skin, xanthoma formation in the intima of the blood vessels and the endocardial lining of the heart and xanthomas in the lining of the bile ducts. In contrast to previous opinion, the xanthoma formation in the lining of the bile ducts, with resulting obstruction, is not considered the cause of xanthomatous biliary cirrhosis, since it was not found in 3 cases at autopsy.[78] For this reason it is believed that xanthoma formation in the lining of the bile duct may occur in rare cases, similar to atheroma formation in arteries, as one of the possible features of but not as the cause of the disease.

Impaired excretion due to hepatitis. In almost all cases of epidemic hepatitis or of toxic hepatitis in its acute or chronic stages, the total cholesterol in the serum is increased. The value of cholesterol present as esters in the serum (normally 70 to 75 per cent of the total cholesterol) decreases in proportion to the severity of the acute liver-cell damage. During convalescence the total cholesterol, as well as the cholesterol present as esters, gradually returns to normal. In chronic hepatitis the values for the total cholesterol are slightly increased, whereas the cholesterol present as esters remains low. In acute yellow atrophy of the liver the total cholesterol is below normal, signifying that insufficient functioning liver parenchyma remains for cholesterol synthesis. In these cases the lowest cholesterol values are observed.[70]

Mechanical obstruction of common bile duct. This condition, due to stone, inflammation or tumor, results in a retention of all bile constituents and consequently of cholesterols. The serum of patients

*Pericholangiolitic miliary cirrhosis.

suffering from mechanical obstruction of bile ducts does not usually show extremely high cholesterol figures (one or two times normal). The ratio of cholesterol to cholesterol present as esters is altered only if acute or chronic damage of the liver cells accompanies the mechanical obstruction.[70, 79–83]

Hypercholesteremia of greater degree (three or four times normal) may develop after injury of the common bile duct during an operation resulting in its complete obliteration. Notwithstanding complete obstruction of long duration, skin xanthomas usually do not develop. The occurrence of secondary xanthomas has been reported only rarely, and these have disappeared after the patency of the common duct has been restored.[76]

Hyperlipemia. The cholesterol content of the blood serum may be increased without functional or mechanical impairment of cholesterol excretion in cases in which hyperlipemia (creamy serum) occurs. Hyperlipemia may be due to an increased transportation or diminished deposition of neutral fat, as pointed out above. Whenever neutral fat increases in the serum, cholesterol accompanies the neutral fat and results in an increase of free cholesterol and cholesterol esters. In such cases foam cells are caused by an increased uptake of fat and cholesterol from the serum (cholesterol infiltration) and are observed especially in the skin and to a minor degree scattered in the spleen, liver and lungs.

The clinical syndromes in which xanthoma formation secondary to hyperlipemia may be encountered are as follows: idiopathic hyperlipemia with secondary xanthomatosis (slight diabetes may or may not be present; the hyperlipemia and xanthomas disappear after neutral fat is restricted in the diet; insulin is not effective in the treatment of hyperlipemia in these cases)[5a]; hyperlipemia with secondary xanthomatosis due to untreated severe diabetes mellitus[84] (insulin treatment alone corrects the diabetic condition as well as the hyperlipemia, and the xanthomatous eruption consequently disappears); idiopathic familial hyperlipemia[2–5] (these cases are favorably influenced by a diet low in fat; the hyperlipemia never completely disappears but is considerably reduced); idiopathic hyperlipemia, hepatosplenomegaly and secondary xanthomatosis with hepatosplenomegaly of the Bürger–Grütz type[6] (this is probably a variation of the syndrome, idiopathic hyperlipemia); hyperlipemia in chronic pancreatitis (this may cause secondary xanthoma formation in rare cases[10–12]); and hyperlipemia in severe cases of glycogen-storage (von Gierke's) disease (the occurrence of secondary xanthoma in this disorder is rare[13–15]).

Hypothyroidism. In cases of hypothyroidism the cholesterol content of the serum is elevated. The reason for this increase is not known. Thyroid medication reduces the cholesterol level of the serum in these patients. In rare cases of hypothyroidism with high serum cholesterol levels, foam cells with xanthoma formation may be found in the skin.[85] Neutral fat and total phospholipids are not increased or show only a slight rise.[86] In hyperthyroidism the total cholesterol level in the serum is a low normal or sometimes below normal. The cholesterol-cholesterol ester ratio in hypothyroidism and hyperthyroidism is normal.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 33401

PRESENTATION OF CASE

A thirty-year-old housewife entered the hospital because of shortness of breath and a mass on the chest wall.

The patient had experienced episodes of dyspnea with emotional stress for three years. A year before admission she had been seen in the Out Patient Department, and the dyspnea was thought to be due to an anxiety state. No mass was noted at that time, although the patient stated that she had first noted it following a fall eighteen months before admission. The mass continued to grow and became tender. She noted weakness for several months and lost 5 to 10 pounds. A month before admission she was seen at another hospital, where a mass was observed over the left seventh rib anteriorly and bloody fluid was removed from the left pleural space. For three days prior to admission she had chills and fever.

Physical examination revealed an acutely ill woman perspiring freely. Over the left seventh rib anteriorly near the costal margin was an extremely tender, hard, fixed mass 6 by 4 by 3 cm. The left side of the chest was flat to percussion, with absent breath sounds posteriorly on the left.

The temperature was 99.6°F., the pulse 100, and the respirations 20. The blood pressure was 110 systolic, 70 diastolic.

The urine had a specific gravity of 1.014 and contained no albumin, and only rare white cells and granular casts were observed in the sediment. Examination of the blood revealed a red-cell count of 3,200,000, with 11 gm. of hemoglobin, and a white-cell count of 11,500. The total protein was 6.3 gm. per 100 cc.

On the first hospital day 100 cc. of serosanguineous fluid was removed from the left pleural cavity. The specific gravity was 1.022. On smear no tumor cells were seen. An x-ray film of the chest following the tap showed fluid in the left pleural cavity forming a fluid level opposite the tenth vertebral body posteriorly. A moderate pneumothorax was present on the left. The heart and mediastinum were displaced to the right. The left lower lobe was collapsed. There was mottling of the bone structure of the anterior portion of the seventh rib with some new-bone formation.

On the second hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. CLIFFORD C. FRANSEEN: The significant findings from which we may get some leads are: the age of the patient (thirty years), the duration of the symptoms, — there is some question whether it was three years or eighteen months before admission, when she had the fall, that she first noticed the mass, — the slight fever, the extremely tender character of the mass on the chest wall, the probable secondary anemia, the elevation of the white-cell count, the exudative character of the pleural fluid that was removed and the fact that the lesion in the rib showed bone destruction and some new-bone formation. In every case of this kind, with a lesion in the bone, we have repeatedly emphasized the importance of reviewing the case from several aspects. In the first place, is it a neoplasm, and if it is neoplastic, is it primary or metastatic? If primary, is it benign or malignant? Then, is it an inflammatory or granulomatous lesion, or does it have a metabolic basis? One by one, we try to exclude these possibilities and to arrive at some conclusion regarding the character of the lesion.

When this patient was seen a year previously in the Out Patient Department no mention was made of an x-ray examination. Of course, that was the time to take an x-ray film. The patient had been aware of the mass six months previously. This lesion might have been discovered at that time.

If we consider neoplasm, was it primary? It could have been primary in the rib or perhaps, from this description, in the pleura, and there is a remote possibility that it was in the lung. Primary tumors of the pleura are quite rare, of course. Secondary invasion of the rib or destruction of the rib, from a pleural tumor, is not common, and altogether the picture does not fit too well with primary tumor of the pleura. Among the tumors of the pleura, the so-called "endotheliomas" are the most frequent. They may produce pleural effusion, but usually not of such a high specific gravity as the tumor in this case showed.

The primary tumors of the rib must, of course, be considered more seriously. It might be well to look at the x-ray films, because they are important in a case of this nature.

DR. STANLEY M. WYMAN: The films, taken six days apart, show fluid in the left pleural cavity with a small amount of air above. The rib detail is unsatisfactory in the first two films but suggests on the later films some mottling and destruction in the body of the rib. The distal 5 or 7 cm. of the rib shows multiple destructive areas in the body of the

medulla, with some periosteal reaction. There is slight bone reaction with increased density in the rib.

DR. FRANSEEN: Is there any expansion of the cortex?

DR. WYMAN: It does not appear to be expanded.

DR. FRANSEEN: So far as the x-ray studies are concerned the important findings include a bone-destructive lesion that is producing new bone. Among the primary tumors of the rib one must consider almost the entire field. Osteogenic sarcoma of the rib, of course, is quite rare. In this group, the chondrosarcomas are more frequent. They can, of course, be osteoplastic and produce new bone, but my impression is that the new-bone formation would be of a different type than that seen in the case under discussion, which is somewhat irregularly distributed. Multiple myeloma is a fairly common tumor of the rib, but it is a purely destructive lesion, almost without exception, and it does not form new bone. Pathologic fractures in these latter lesions are very common, but there is no fracture here or thinning to any extent. Hodgkin's disease, in particular, may affect the rib but usually in the late stages of the disease, and we have no real evidence for including that lesion.

Ewing tumor is not an uncommon lesion at this site and may produce new-bone formation with effusion into the chest cavity. I do not see how one can entirely exclude that possibility.

Metastatic lesions of the rib are perhaps the most frequent statistically. This patient was a relatively young woman, and we have no evidence for considering a metastatic lesion on the basis of the data provided us. Metastatic lesions of this type usually do not produce new bone in a rib.

We must consider inflammatory lesions seriously because of the extremely tender character of the mass, the slight fever and some leukocytosis. Many of the slowly developing, inflammatory lesions of bone can produce both bone destruction and new-bone formation. Some of the granulomatous types, like syphilis, might be considered, and although no serologic findings are reported, there is no reason for considering syphilis seriously. I mention it because almost all bone tumors may on occasion be simulated by syphilis or by tuberculosis, which can perhaps also be excluded.

We then come to a consideration of chronic osteomyelitis. This must have been a relatively chronic process, with an acute episode toward the end, with chills and fever and with exudate in the pleural cavity. We know that chronic osteomyelitis may persist in bones like this for a long time with relatively little reaction. The patient had a fall with apparent injury at that site, although not necessarily, because after a fall people feel themselves all over and discover masses that were present prior to the injury. Women, particularly, are apt to discover masses in the breast under such circumstances and to say that the mass was due to a fall.

There are diseases such as eosinophilic granulomas of the rib, which are quite rare, and I am not familiar with all the variants that can occur in them because of the paucity of cases that have been recorded. Whether it can simulate this lesion, I am not prepared to say. A biopsy would be necessary to establish these diagnoses.

So far as metabolic lesions go, we have nothing in the report to suggest that this lesion had a metabolic basis. The only blood chemical finding reported is the total protein, which was not remarkable. That determination is important, of course, in the consideration of multiple myeloma, in which it is almost always elevated.

In putting all these facts together we find that the duration was relatively long for a malignant process in the rib. If it were a malignant tumor, it would have to be relatively slowly growing. I cannot escape the impression that this was an inflammatory lesion — probably some form of chronic osteomyelitis, with late pleural effusion. The fluid may have been present for a longer time, but it was the pleural reaction that brought the patient to the hospital. If I had to choose among these various diagnoses, I should put osteomyelitis first, but with the reservation that many of the other lesions that I have mentioned cannot be excluded except by biopsy.

CLINICAL DIAGNOSIS

Ewing tumor?

DR. FRANSEEN'S DIAGNOSIS

Chronic osteomyelitis of rib.

ANATOMICAL DIAGNOSIS

Ewing tumor of rib and phalanx of toe.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: This lesion was first aspirated with a large needle, and all that could be removed was some connective tissue in which there were a few deeply stained cells that we could not make anything of. They were apparently traumatized in the aspiration biopsy, and we believed that the biopsy was inadequate to make a diagnosis. The patient was then admitted to the hospital, and an open biopsy performed, which showed a Ewing tumor of a rather typical form, but without, at least in our biopsy, any evidence of reaction.

A week after the biopsy the right fourth toe became painful and swollen. The patient stated that this had occurred intermittently for about a year. An x-ray film was taken, and Dr. Wyman will show the films.

DR. STANLEY M. WYMAN: The proximal phalanx of the fourth toe shows multiple rather cyst-like areas that are, however, very ill-defined but somewhat indicative of destruction. There is a slight suggestion of a little periosteal reaction.

DR. CASTLEMAN: Will you discuss the lesion in the toe, Dr. Franseen?

DR. FRANSEEN: It is unfortunate that the patient did not have this four days earlier because with a multiplicity of lesions, I should have been more willing to accept a diagnosis of Ewing tumor. We know that Ewing tumor, more frequently than any other bone tumor, produces a response suggestive of inflammation in these various sites, and the appearance of this additional lesion would be entirely consistent with it.

DR. CASTLEMAN: Have you ever seen metastases of Ewing tumor in the phalanges?

DR. FRANSEEN: I do not remember that I have seen one.

DR. WYMAN: I think that they are extremely rare, but I believe that we have seen one.

From the x-ray films I should not have thought that the lesion in the toes was Ewing tumor. The rib is consistent with it, but the toe is an unusual location.

DR. FRANSEEN: I should certainly not be able to make a diagnosis from this x-ray film of the toe.

DR. CASTLEMAN: The toe was amputated and also proved to contain a Ewing tumor. I believe that it is the first one we have seen in this location; Geschickter* mentions a few in the tarsus and metatarsus but none in the phalanx. The fact that no lesions are seen on the films of the other bones raises the remote possibility that the toe lesion was another primary tumor. The chances are, however, that this is the first of other metastases that will become evident later. The patient is receiving x-ray treatment over the rib.

*Geschickter, C. F., and Copeland, M. M. Tumors of bone. *Internat. S. Digest* **10**:323-343, 1930.

CASE 33402

PRESENTATION OF CASE

A fifty-four-year-old married woman entered the hospital with the complaint of lower abdominal cramps of two days' duration.

The present illness began abruptly about forty-eight hours before admission. There were severe lower abdominal cramps with continuous aching and a sense of fullness. The patient was nauseated and vomited several times without relief. There was no change in bowel habit, and no urinary symptoms were noted. She felt feverish but had no chills. She was seen by a physician, who noted a mass in the lower abdomen. Pelvic examination revealed a firm, somewhat movable and tender tumor about the size of an orange occupying the apex of the vagina in the region of the cervix; no other mass could be felt. The pain was relieved temporarily by morphine but recurred. Hospitalization was advised.

The patient's health had always been excellent. An appendectomy had been performed twenty-seven years before admission. The menstrual history was normal. She had had two children without complication. Two years before admission the menstrual periods had ceased. There was moderate annoyance from hot flashes and sweats, and she had severe mental depression. These symptoms were relieved by estrogens, and some form of hormone therapy had been administered up to the time of admission to the hospital. Approximately four months before admission conization of the cervix was carried out to relieve a complaint of vaginal discharge.

Physical examination disclosed a flushed and somewhat dehydrated woman in some distress. The abdomen was soft, and peristalsis was normal. There were tenderness and a sense of an asymmetrical mass in the suprapubic area. Pelvic examination was essentially as described above.

The temperature was 99.4°F., and the pulse and respirations were normal. Examination of the blood revealed a hemoglobin of 11.6 gm. and a white-cell count of 8700. A catheter specimen of urine showed no albumin or sugar; the sediment contained rare red cells and 12 white cells per high-power field. Cytologic examination of the vaginal secretion was negative.

There was no change in the patient's condition overnight. On the day following admission an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. FRANCIS M. INGERSOLL: The tender, movable mass occupying the apex of the vagina must have accounted for the symptoms of the low abdominal cramps and a sense of fullness. The description of the pelvic examination failed to note if the cervix was present in addition to the mass or whether this mass was actually the cervix. No mention was made of the size, shape or position of the uterus, although a symmetrical mass in the suprapubic area was described. The uterus and cervix must have been present, since the only previous operation was an appendectomy. To arrive at a diagnosis in this case it is necessary only to decide what the mass in the pelvis was.

This mass seemed to be so close to the vagina that an ovarian tumor can probably be ruled out. If the patient had had a previous total hysterectomy the mass could have been an ovarian tumor adherent to the vaginal apex, but since the uterus was apparently still present, ovarian tumors could not have occupied this position.

A vaginal cyst or tumor displacing the cervix and uterus is a possibility. Gartner's duct — a tube that is the homologue of the vas deferens, and a relic of the embryonic wolffian duct — occasionally causes cystic masses in the vagina, but they are usually on the lateral vaginal wall, rarely cause pain and

should have been discovered at the conization operation four months previously. Inflammatory masses are ruled out by the lack of fever and the normal white-cell count.

The field is narrowed down, then, to some lesion of the cervix itself. Cervical fibroids sometimes distort the entire organ and may become orange sized, but the patient was fifty-four years of age and fibroids do not develop in that age group, since it must be assumed that they were not present four months previously.

An enormous Nabothian cyst might feel like this tumor at the apex of the vagina. These cysts are unlikely to reach such a size. Moreover, two facts in the history can be correlated to account for this mass in the vagina: the patient had had a conization of the cervix, and she had been taking estrogens for hot flashes and mental depression. A common occurrence after estrogen therapy is uterine bleeding. No mention of any postmenopausal bleeding is found in the record. A frequent complication following conization of the cervix is stenosis of the cervical canal, with trapping of blood in the uterus. A distention of the cervical and endometrial canals occurs, causing pain and a sense of fullness in the pelvis. This diagnosis of cervical occlusion with distention of the cervical and endometrial canals with blood best explains the clinical picture in this case.

Clinical Diagnosis

Hematometrium due to cervical stenosis.

Dr. Ingersoll's Diagnosis

Hematometrium due to cervical stenosis.

Anatomical Diagnoses

Hematometrium due to cervical stenosis.
Adenomyosis of uterus.

Pathological Discussion

Dr. Benjamin Castleman: Will you tell us what was found at operation, Dr. Ulfelder?

Dr. Howard Ulfelder: Under anesthesia one could easily feel a movable, smooth, rounded pelvic tumor about the size of a grapefruit. It was palpable in the suprapubic region and presented at the apex of the vagina as a fluctuant, rounded surface with no sign of the cervix. One small dimple suggested the external os. A needle inserted here aspirated dark blood. The opening was enlarged, and free drainage allowed for a large hematometrium.

Eight days later an abdominal hysterectomy was performed. The uterus had shrunk to normal contour and was easily removed, together with the cervix.

Dr. Castleman: On opening the specimen it was apparent that the cervix was markedly constricted at the external os and had been greatly expanded and thinned out by the accumulating secretions and blood. The fundus had been only slightly involved and had risen on top of the expanding cervix. Microscopically, the area of stenosis showed only chronic inflammation. The myometrium was extensively involved with adenomyosis.

Dr. Ulfelder: Stenosis of the cervix followed by hematometrium or pyometrium is a complication not infrequently seen after application of radium or cauterization. It may occur without antecedent trauma as a result of menopausal atrophy alone. This is particularly true in patients in whom estrogen bleeding is induced after years of inactivity. Dr. Ingersoll has emphasized the point that a combination of trauma to the cervical canal and uterine bleeding due to estrogens is the most frequent history in these cases. The usual site of stricture is at the internal os, since the canal is narrowest at this point, and in such cases a dilated and thinned uterine body with an undistorted cervix is still found to be present in the usual position. Occlusion at the external os, as in the case under discussion, is rare.

Although adequate drainage is easily established, two points must be kept in mind during the treatment of this condition: cancer as the cause of obstruction must be excluded, and there is a tendency for the inflammatory stenosis to recur if the uterus is not removed. If hysterectomy is not planned a rubber T-tube catheter should be left in the fundus with the long arm out through the cervical orifice for at least three months, until a permanent channel can be established.

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RED CROSS NATIONAL BLOOD PROGRAM

The plans of the American Red Cross to administer and finance a program designed to provide, without charge, blood and its derivatives for all the people of the United States* is a fitting climax to the magnificent job done by this organization during the war. The extent of the program is indicated by the estimates that, eventually, about four million pints of blood will be needed annually and that nearly $20,000,000 will be required each year to cover all costs. The great value of blood and its derivatives in the saving of human lives has been proved, particularly during the war, and there can be no doubt that a national enterprise of this sort is badly needed. Nor is there any question that the American Red Cross, which supplied more than thirteen million pints of blood to the armed forces, is best qualified to undertake this gigantic effort as a peace-time service.

Four distinct phases are involved in the program: collection of the blood; its processing, packaging and storage; its distribution; and continuous research and investigation of the quality of the products and their proper usage. In addition to whole blood, the following derivatives will be provided: plasma serum albumin, immune serum globulin, antihemophilic globulin, blood-grouping serums, fibrin films and red-cell suspensions, paste and powder. Other products will undoubtedly be made available as soon as their usefulness in medicine and surgery has been proved. Under the guidance of the national organization, the general plan of operation will be handled by the Red Cross chapters, which will work in co-operation with the medical societies, public-health agencies, hospitals and other institutions in their communities.

It is expected that state or community programs already established will be given a further impetus through integration with the national endeavor to provide a greater variety of blood derivatives. In Massachusetts the burden of establishing such a program has been largely borne by the Department of Public Health and hospital and medical groups, the role of the Red Cross having been that of donor procurement and certain nontechnical local assistance. With the undertaking of a blood program as a major activity of the American Red Cross, it may be possible to extend the program in Massachusetts, which, with the limited funds at present available, has never been able to catch up with the ever-growing requirements for blood and blood products in the Commonwealth.

A program such as this demands constant support of all concerned with it — as physicians or patients or in other capacities. The only way of ensuring the success that the endeavor must achieve if the needs for blood are to be met is for all concerned to give active aid and encouragement to every effort designed to make more blood available.

To put this program in operation in all sections of the United States will be difficult and will require time. But the benefits that will accrue are incalculable: there is no means of measuring the value

*McGinnes, G. F. National blood program inaugurated. *Red Cross Courier* 27:3 (July), 1947.

of the lives that will be saved and the suffering that will be alleviated by the immediate provision of blood and its derivatives, without cost, to the ill and injured. It is a typical undertaking of the American Red Cross in its goal to be of service to humanity, and it deserves enthusiastic and wholehearted support by all.

EPIDEMIOLOGY OF NEONATAL SKIN INFECTION

A RECENT paper by Allison and Hobbs* presents an interesting study on the epidemiology of pemphigus neonatorum. This investigation, conducted between November, 1943, and November, 1945, in the nursery of a maternity unit in Cardiff, Wales, was occasioned by a recent considerable increase in the infection, particularly in the nurseries of this and similar obstetric hospitals.

During the period of the investigation 2719 infants were born in or admitted to the hospital; of these, 111 (4.1 per cent) developed pemphigus. In addition, 25 cases of staphylococcal conjunctivitis occurred, either alone or in association with the pemphigus.

It is notoriously difficult to trace staphylococcal migrations on account of the varieties of strains and the ubiquity of the organisms. The study was nevertheless attempted, painstakingly and meticulously, with culturing of the lesions, the noses, the eyes and, in some cases, the umbilici of the infants, of the noses and the throats of the mothers, doctors, attendants and nurserymaids, of the air and the dust of the nursery, and of the blankets and the gowns. The infecting organism, a coagulase-positive staphylococcus, frequently in pure culture, was obtained from every lesion investigated, and the strains were checked serologically. A low correlation was found between mothers and infants: rarely a mother developed a sore throat, apparently from her infected infant, and the converse was never noted. But the organism was found to be widespread in the infants' environment, being recovered from the noses and throats of some of the healthy infants, from the blankets, gowns, dust and air and particularly, from a high proportion of the noses of the nursing staff. It must be admitted that nursery conditions during most of the period of the study were not good, since the nursery was badly overcrowded, as well as poorly lighted and ventilated because of air-raid precautions.

The implications of this study are obvious, and they give added emphasis to knowledge already possessed regarding discharges from the human nasopharynx. These constitute a significant, if not the most important, source of staphylococcal, streptococcal and other infections of this type, and the carrier, regardless of the precautions taken, has no place in an infant nursery or surgical operating room or ward or, indeed, in any manner of close contact with other persons. No great imagination is necessary to conjure up a number of links in the chain of infection — the iniquitous pocket handkerchief, with hands unwashed after its use, the popular swimming pool or bathing pond and the family toothbrush holder.

In the nursery nothing can take the place of adequately developed consciences and a technic that has become automatic through intensive training. This study introduces further evidence in favor of the isolated mother-infant unit in maternity departments.

*Allison, V. D., and Hobbs, B. C. Inquiry into epidemiology of pemphigus neonatorum. *Brit. M. J.* 2:1-7, 1947.

MASSACHUSETTS MEDICAL SOCIETY

BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

DEATHS

POTTER — Lester F. Potter, M.D., of New Bedford, died on August 17. He was in his seventy-fifth year.

Dr. Potter received his degree from Bowdoin Medical School in 1897. He was a member of the New England Otological and Laryngological Society.

SHATSWELL — James A. Shatswell, M.D., of Beverly, died on August 26. He was in his eighty-fourth year.

Dr. Shatswell received his degree from College of Physicians and Surgeons of Baltimore in 1890.

His widow and a brother survive.

SPIEGL — Erwin D. Spiegl, M.D., of Lynn, died on April 6. He was in his forty-sixth year.

Dr. Spiegl received his degree from Deutsche Universität Medizinische Fakultät, Prague, Czechoslovakia, in 1928. He was a member of the staff of the Lynn Hospital.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

Clinic	Date	Clinic Consultant
Salem	Oct. 6	Paul W. Hugenberger
Brockton	Oct. 9	George W. Van Gorder
Gardner (Worcester Subclinic)	Oct. 14	John W. O'Meara
Pittsfield	Oct. 15	Frank A. Slowick
Worcester	Oct. 17	John W. O'Meara
Greenfield	Oct. 20	Charles L. Sturdevant
Springfield	Oct. 21	Garry deN. Hough, Jr.
Hyannis	Oct. 23	Paul L. Norton
Fall River	Oct. 27	David S. Grice

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments.

BOOK REVIEWS

The Journals and Letters of the Little Locksmith. By Katherine B. Hathaway. 8°, cloth, 395 pp., with 17 illustrations by the author. New York: Coward-McCann, Incorporated, 1946. $3.75.

Anyone who is interested in psychiatry will find this book revealing, and if the reader is concerned with the psychology of literary artists, he may find it doubly interesting. It presents the intimate story of a remarkable life spent struggling first with a severe deformity of the spine and then with the host of secondary problems that resulted from being "The Little Locksmith," which was the way in which the author chose to think of her disability. The psychological benefits from the illness compensated only partly for the original injury to her personality, and these compensations in turn led to complicated emotional situations, which she describes in this book with unusual skill and some insight. She records her sensitive reactions and displays dynamic patterns in her behavior so carefully that the perceptive reader will be well repaid for the time he spends on the book.

One must read *The Little Locksmith*, an earlier book by the same author, to appreciate the full power and courage of this extraordinary woman, who in some ways resembles Katherine Mansfield, although Katherine Hathaway had more to endure in the way of physical hardship. The setting of her story is Salem, Massachusetts, but it also takes in Cambridge and Boston, of course, as well as Maine and travel in Europe.

Miss Hathaway's whole life was spent more or less in the care of medical specialists from spine to soul straighteners. She lived first in a Bradford frame and then in a body brace for years. She had to take special exercises all her life, and could rest and work only in certain strained positions. In her younger days she had a psychoanalysis with Dr. Izette DeForest, followed later by eclectic psychotherapy with Dr. Merrill Moore, who encouraged her in the writing of books. For the preservation and editing of her manuscripts, credit is due her brother, Warren H. Butler, of Salem, who, serving effectively in the role of literary executor, has made her books available to the public — Katherine Hathaway died in the prison of her deformed body on Christmas Eve, 1942, just before her first book was published, with heart failure due to increasing restriction of the heart and lungs secondary to the spinal curvature. *The Little Locksmith* immediately became a literary success and a Book-of-the-Month Club choice. She was showered with posthumous literary recognition. Her legend, as one of America's most unique woman writers, is now growing to such an extent, particularly in New England literary circles, that she is already a myth and may become a cult in a small way, especially among physically handicapped persons. Few people writing in recent years have recorded with such sincerity and vitality their innermost thoughts, and few have left such an inspiring and beautiful documentation of their passage through life.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Clinical Allergy: A monograph on the management and treatment of allergic diseases. By Alexander Sterling, M.D. With the assistance of Bea Sterling Hollander, M.D. 8°, cloth, 198 pp., with 16 illustrations. New York: International Universities Press, 1947. $5.00.

This manual discusses clinical allergic problems, especially from the viewpoint of diagnosis and therapy. The text is amplified with 51 case histories illustrative of various conditions. The price seems excessive for this small volume.

Gynecology, with a Section on Female Urology. By Lawrence R. Wharton, Ph.B., M.D., assistant professor of gynecology, Johns Hopkins Medical School, assistant acting gynecologist, Johns Hopkins Hospital, and consultant in gynecology, Union Memorial Hospital, Hospital for the Women of Maryland and Church Home and Infirmary. Second edition. 8°, cloth, 1027 pp., with 479 illustrations. Philadelphia: W. B. Saunders Company, 1947. $10.00.

This second edition of a standard textbook, first published in 1943, has been revised to date. The sections on embryology and congenital malformations have been reorganized and rewritten. The technic of ureterotomy for ureteral stone has been amplified. A chapter on water cystoscopy, written by Dr. Charles L. Prince, has been added to the section on female urology, and a separate chapter has been devoted to the female urethra. New illustrations have been included in connection with new developments in operative technic.

NOTICES

ANNOUNCEMENT

Dr. Frank B. Colloten announces the removal of his office to 73 Bay State Road, Boston.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9-10 a.m.

Medical Conference Program

Wednesday, October 8 — The Pulmonary Segment as a Unit for Treatment. Dr. Richard H. Overholt.
Friday, October 10 — Pulmonary Embolism. Dr. Lewis Dexter.
Wednesday, October 15 — Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.
Friday, October 17 — Gastritis. Dr. Seymour Gray.
Wednesday, October 22 — Uterine Retrodisplacements. Dr. George A. Bourgeois.
Friday, October 24 — Traumatic Shock: The physiologic effects of blood loss. Dr. F. A. Simeone.
Wednesday, October 29 — A Discussion of Clinical Otosclerosis with Demonstration of the Fenestration Operation. Dr. Philip E. Meltzer.
Friday, October 31 — Precautions in Handling Radioactive Materials in Medical Research. Dr. Shields Warren.

On Tuesday and Thursday mornings from 9:00 to 10:00 Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Friday afternoons from 2:00 to 4:00 therapeutic conferences will be held with round-table discussion, Dr. R. P. McCombs, Moderator. On the second and fourth Friday afternoons of each month, Dr. Merrill Sosman will conduct x-ray conferences from 4:00 to 6:00. On Saturday mornings from 9:00 to 10:00, clinics will be given by Dr. William Dameshek. Medical rounds are conducted each weekday except Saturday by members of the Staff from 12:00 to 1:00.

All exercises are open to the medical profession.

NEW ENGLAND DERMATOLOGICAL SOCIETY

A regular meeting of the New England Dermatological Society will be held at the New Haven Hospital, New Haven, Connecticut, on Wednesday, October 8, at 2:00 p.m. The meeting is open only to members and invited guests.

HARVARD MEDICAL SOCIETY

The first meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, October 14, at 8 p.m. Members of the Biophysical Laboratory of Harvard Medical School will present a symposium entitled "Biological Problems Studied with Isotopes."

PROGRAM

Rates of Biological Processes in the Intact Animal. Dr. DeWitt Stetten, Jr.

Some Aspects of the Metabolism of Zinc as Studied with the Radioisotope Zn^{65}. Drs. John G. Gibson, 2nd, and Bert L. Vallee.

The Incorporation of Alanine into Protein. Drs. Ivan D. Frantz, Jr., Robert B. Loftfield and Warren W. Miller.

Tracer Studies of Gas Exchange in Man. Drs. A. C. Barger and E. M. Landis.

Some Studies in Radioautographs. Drs. A. K. Solomon and J. C. Cobb.

Subsequent meetings will be held on November 4 and December 19, 1947, and January 13, February 10, March 9, April 13 and May 11, 1948.

JOINT MEETING OF NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS AND AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INCORPORATED

A joint meeting of the New England Society of Anesthesiologists and the American Society of Anesthesiologists, Incorporated, will be held in Boston on November 10.

PROGRAM

8 a.m. to 12 m. Clinical demonstrations in operating rooms of the Massachusetts General Hospital, Massachusetts Memorial Hospitals, St. Elizabeth's Hospital, New England Deaconess Hospital, New England Baptist Hospital and Boston City Hospital.

12:30 p.m. to 1:30 p.m. Informal luncheon at the Hotel Sheraton.

2:00 p.m. Scientific program at the Hotel Sheraton. Dr. Julia G. Arrowood will speak on "Pain Mechanisms." Drs. William H. Sweet and William T. Chapman will lead the discussion.

3:00 p.m. Dr. L. K. Diamond will speak on the subject "Whole-Blood Transfusions and Untoward Reactions," which will be discussed by Dr. C. P. Emerson.

7:00 p.m. Dinner at the Hotel Sheraton. Dr. B. B. Raginsky, of Montreal, Canada, will speak on the subject "Mental Suggestion as an Aid to Anesthesia."

INCREASED PAY FOR MEDICAL OFFICERS

According to a recent announcement by Major General Raymond W. Bliss, Surgeon General of the Army, all officers of the Regular Army Medical and Dental Corps, as well as all medical and dental officers serving voluntarily on extended active duty, will be paid an additional $100 a month. This addition to the incomes of such officers is regarded by the War Department "not as a pay increase but as an equalization measure designed to bring the incomes of Medical and Dental Corps officers more nearly in line with those of civilian doctors and dentists."

The additional compensation will be paid not only to officers who were on extended active duty as of September 1, 1947, the effective date of the enabling legislation, but also to eligible officers of the Medical and Dental Corps who are commissioned in the Regular Army or who volunteer for extended active duty within the next five years. The duration of these benefits is limited to thirty years of active service.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 9

FRIDAY, OCTOBER 10

*9:00–10:00 a.m. Pulmonary Embolism. Dr. Lewis Dexter. Joseph H. Pratt Diagnostic Hospital.

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

MONDAY, OCTOBER 13

*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, OCTOBER 14

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

8:00 p.m. Harvard Medical Society. Amphitheater, Building D, Harvard Medical School.

WEDNESDAY, OCTOBER 15

*9:00–10:00 a.m. Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon. Joseph H. Pratt Diagnostic Hospital.

*12:00 m. Grand Rounds and Clinicopathological Conference. (Children's Hospital). Amphitheater, Peter Bent Brigham Hospital.

*Open to the medical profession.

OCTOBER 6–10. American Public Health Association. Page 456, issue of March 20.

OCTOBER 6–17. New York Academy of Medicine. Page 348, issue of August 28.

OCTOBER 8. New England Dermatological Society Notice above.

OCTOBER 8–31. Joseph H. Pratt Diagnostic Hospital. Medical Conference Program. Page 529.

OCTOBER 9. Practical Points in Geriatrics. Dr. Roger I. Lee. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

OCTOBER–DECEMBER. Thirteenth Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital. Page 348, issue of August 28.

OCTOBER 13–18. Medicolegal Conference and Seminar for Pathologists, Medical Examiners and Coroners. Page 242, issue of August 14.

OCTOBER 14. Harvard Medical Society. Notice above.

OCTOBER 29–31. New England Postgraduate Assembly. Copley Plaza Hotel, Boston.

NOVEMBER 10. Joint Meeting of New England Society of Anesthesiologists and American Society of Anesthesiologists, Incorporated. Notice above.

NOVEMBER 13–15. Association of Military Surgeons. Annual Meeting. Hotel Statler, Boston.

FEBRUARY 6. American Board of Obstetrics and Gynecology. Page 242, issue of August 14.

APRIL 19–23. American College of Physicians. Page xiii, issue of July 31.

MAY 6–8. American Association for the Study of Goiter. Part xiii, issue of July 31.

MAY 11–15. American Association on Mental Deficiency. Page 140, issue of July 24.

DISTRICT MEDICAL SOCIETIES

MIDDLESEX EAST

NOVEMBER 19.
JANUARY 21.
MARCH 24.
MAY 12. Annual meeting.
All meetings will be held at the Bear Hill Golf Club.

NORFOLK

OCTOBER 28. Lahey Clinic Night.
NOVEMBER 25. Tufts Night.
JANUARY 27. Round-Table Discussion: Bleeding from the Alimentary Tract.
FEBRUARY 24. Obstetric and Gynecologic Night.
MARCH 23. Harvard Night.

PLYMOUTH

OCTOBER 16. Jordan Hospital, Plymouth.
NOVEMBER 20. Plymouth County Sanatorium, South Hanson.
JANUARY 15. Brockton Hospital, Brockton.
FEBRUARY 19. Toll House, Whitman.
MARCH 18. Goddard Hospital, Brockton.
APRIL 15. State Farm, Bridgewater.
MAY 20. Lakeville Sanatorium, Lakeville.

SUFFOLK

DECEMBER 4. Censors' Meeting.

WORCESTER

OCTOBER 8. Rutland State Hospital.
NOVEMBER 12. Grafton State Hospital.
DECEMBER 10. Worcester City Hospital.
JANUARY 14. St. Vincent's Hospital.
FEBRUARY 11. Worcester State Hospital.
MARCH 10. Memorial Hospital.
APRIL 14. Hahnemann Hospital.
MAY 12. Annual Meeting.